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Annual Report of
Intramural Research

October 1, 1988
to
September 30, 1989

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00070-16 BP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychological and Biological Interactions in the Mood and Anxiety Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Robert M. Post, M.D.	Chief	BPB NIMH
Dr. R. Cohen	Laboratory of Cerebral Metabolism, NIMH	
Dr. L. DeLisi	Dept of Psychiatry, State University of N.Y.	
Dr. T.W. Uhde	Biological Psychiatry Branch, NIMH	

COOPERATING UNITS *(if any)*

BPB,CNB,NSB,NPB,LCM,LDP,LPP,RSB,IRP, NIMH; DEB,NICHD; IRP, NIAAA; MN, NINCDS; PDS, NIH; USUHS, Dept of Def.; U. of CA; Tufts U.; U. of S.Carolina Med. Sch.; INSERM; St. E.'s Hosp.; St. Michael's Hosp.; SUNY; U. of Wash.; Beth Israel Hosp.

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Section on Psychobiology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
9.0	5.0	4.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Evaluation, study, and treatment of patients with manic-depressive and schizoaffective illness are the primary goals of the Section. Double-blind, placebo-controlled clinical trials are employed to evaluate routinely used and novel agents for the treatment of these disorders. Anticonvulsants such as carbamazepine have been demonstrated to be clinically effective in the acute and prophylactic treatment of manic-depressive illness. We have identified possible clinical and biochemical markers of response to lithium versus carbamazepine and other agents. For example, antimanic responders to carbamazepine appear to be more severely ill, more dysphoric, and more rapidly cycling than non-responders, i.e., variables that tend to be associated with lithium nonresponse. In attempting to elucidate possible mechanisms of action, we have found that alpha-2 noradrenergic and "peripheral-type" benzodiazepine receptor mechanisms may be important to the anticonvulsant if not the psychotropic effects of carbamazepine. Other neurotransmitter, modulator, and peptide substances that may account for carbamazepine's positive effects on mood and behavior are being studied. The Section also seeks to identify regional alterations in brain electrophysiological and metabolic activity that are related to changes in behavior and cognition in affective illness. A clinical probe of limbic system excitability utilizing a novel provocative agent, procaine, is also being employed. Procaine selectively increases fast activity over the temporal lobe in association with a variety of behavioral and cognitive alterations and secretion of cortisol, ACTH, and prolactin. Animal models of electrophysiological and pharmacological kindling and cocaine-induced behavioral sensitization are studied and implicate conditioning and learning processes in the progressive behavioral changes induced. These models may help provide new clinical and biochemical insights into the mechanisms that underlie the progressive and long-term changes in behavior in a variety of clinical syndromes including cocaine-induced psychopathology and affective illness.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00071-09 BP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychobiological Correlates and Treatment of Panic and Related Mood Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

T.W. Uhde, M.D., Chief, Section on Anxiety and Affective Disorders, BPB, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Section on Anxiety and Affective Disorders

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Patients with pathological degrees of anxiety who meet DSM-III-R criteria for panic disorder, with or without agoraphobia; generalized anxiety disorder; or social phobia are evaluated using psychological, physiological, and biochemical methodologies. Patients with major affective illness, particularly those with a significant anxiety component, are also eligible for participation in the program. Particular attention is given to the role of the noradrenergic, dopaminergic, adenosinergic, and serotonergic neurotransmitter systems as assessed by: 1) measurement of the metabolites NE, MHPG, and HVA in plasma; 2) adrenergic receptor number and function in platelets; and 3) neuroendocrine and behavioral responses to the alpha-2 adrenergic agonist clonidine and antagonist yohimbine, the serotonin agonist m-chlorophenylpiperazine (MCPP), and the adenosine receptor antagonist, 1,3,7 trimethylxanthine. Research investigating the relationship of noradrenergic and adenosinergic function to other neurotransmitter systems and the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes also has been initiated. Caffeine and nifedipine challenges are administered to assess their behavioral and biochemical effects. Other approaches to understanding the pathophysiology of anxiety and its potential treatment with alprazolam, carbamazepine, clonidine, dipyridamole, imipramine and verapamil will be explored.

An animal model using genetically "nervous" and "normal" pointer dogs has been developed and studied in relation to noradrenergic and adenosinergic function.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 00180 - 07 BP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Psychobiology and Treatment of Menstrually-Related Mood Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
David R. Rubinow, M.D., Chief, Unit on Peptide Studies, BPB, NIMH

P. Schmidt, M.C. Hoban, M. Jensvold, K. Denicoff, C. Ollo, M. Tancer, M. Stein, BPB, NIMH; G. Merriam, L. Nieman, D. Raben, ERRB, NICHD; R. Elin, CPD, CC; NIH; P. Gindoff, George Washington University, E. Bou, CC, NIH; M. Kaliner, M. Frank, LCI, NIAID; S. Paul, NSB, NIMH; R. Purdy, San Antonio, TX

COOPERATING UNITS *(if any)*

BPB, NSB, NIMH; ERRB, NICHD; CPD, CC, NIH; George Washington University; LCI, NIAID, San Antonio, TX

LAB/BRANCH
Biological Psychiatry Branch

SECTION
Section on Behavioral Endocrinology

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The goals of this project are to detect and accurately describe menstrually-related mood disorders, explore their pathophysiology and response to pharmacological and environmental manipulation, and to document the relationship between reproductive endocrine change and disorders of mood as a way of further investigating the neurobiology of psychiatric illness. The longitudinal screening methods developed by this group are capable of distinguishing women with menstrually-related mood syndromes from those who only believe that they have such a syndrome. With these methods, we have identified the following: 1) the occurrence of the characteristic premenstrual syndrome state during an antiprogestin induced follicular phase; 2) a reduction of PMS symptoms during clonidine infusions compared with placebo in some but not all patients; 3) an absence of difference in red blood cell or mononuclear blood cell magnesium over the menstrual cycle in patients compared with controls; 4) an absence of significant differences in CRH stimulated ACTH in patients compared with controls during the follicular and luteal phases; 5) an approximately 70% prevalence of history of physical or sexual abuse in patients and controls; 6) an increased tendency to dissociate in patients compared with controls, with a significant menstrual cycle phase effect noted in patients but not controls; 7) an absence of a significant correlation between plasma gonadal steroid levels and affective symptoms.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 00181-05 BP

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Hormonal Studies of Affective Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David R. Rubinow, M.D., Chief, Unit on Peptide Studies, BPB, NIMH

Dr. P. Sunderland, LCS, NIMH; Dr. S. Braca, M, SMRC; Dr. K. Denicoff, BPB, NIMH; Dr. P. Hauser, BPB, NIMH; Dr. P. Lewitt, Lafayette Clinic, Detroit MI; Dr. W. Berrettini, CNG, NIMH; Dr. J. Kleinman, IRP, NIMH; Dr. T. Mellman, BPB, NIMH; Dr. M. Demitrack, BPB, NIMH

COOPERATING UNITS *(if any)*
BPB, LCS, CNG, IRP, NIMH; SMRC; Lafayette Clinic, Detroit, MI

LAB/BRANCH
Biological Psychiatry Branch

SECTION
Unit on Peptide Studies

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.0	1.0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies of somatostatin and cortisol in relation to affective and other neuropsychiatric disorders have continued. Additionally, other studies have been undertaken including the investigation of progesterone in women with a variety of affective syndromes, beta endorphin in humans and rats administered interleukin-2 (IL-2), dehydroepiandrosterone-sulfate in Alzheimer's and AIDS patients, and pituitary cell culture response to IL-2.

A) Somatostatin - In human post-mortem regional brain studies, no difference in concentration of somatostatin was observed in the hippocampus, amygdala, or prefrontal region among schizophrenics, suicides, and controls. Post-mortem CSF studies showed significantly increased ventricular CSF somatostatin in Parkinson's and Huntington's patients compared with controls or Alzheimer's patients.

B) Cortisol - Salivary cortisol has been used to study patients and controls undergoing caffeine infusion, patients on carbamazepine, and patients with affective disorder, on a longitudinal basis.

C) Other assay measures - Assays for plasma beta-endorphin, salivary progesterone, and CSF DHEAS have been developed to study IL-2 and menses-related affective changes, as well as AIDS and Alzheimer's disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 00182-06 BP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Behavioral Medicine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David R. Rubinow, M.D., Chief, Unit on Peptide Studies, BPB, NIMH

Dr. Kirk Denicoff, Biological Psychiatry Branch, NIMH;
Dr. Margaret Jensvold, Biological Psychiatry Branch, NIMH;
Dr. Steven Rosenberg, Surgery Branch, NCI;
Dr. Pim Brouwers, Georgetown University
Dr. Clifford Lane, Lab. of Immunoregulation, NIAID;

COOPERATING UNITS *(if any)*
BPB, LNP, OD, NB, CNE, CNB, NIMH; SB, FCRF, D, NCI; LIR, LCI, NIAID; CCM, CC; A&R, LN, NIDDK; MN, NINDS; Georgetown University

LAB/BRANCH
Biological Psychiatry Branch

SECTION
Section on Behavioral Endocrinology

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	1	1

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Eleven protocols are currently active and conducted out of the Consultation-Liaison Service-based behavioral medicine research program. These protocols examine the phenomenology and biological correlates of illness or treatment-induced mood, behavioral, and cognitive changes. The protocols address such areas as: a) the effects of previous psychiatric history on the psychiatric morbidity associated with certain diseases and their treatment; b) the psychiatric phenomenology of certain diseases and their treatment; c) the treatment response characteristics of psychiatric disorders associated with diseases or their treatment; d) biochemical factors that may serve as predictive diagnostic markers for illness or for treatment-associated mood/behavioral or cognitive syndromes; e) the effects of mood state alterations on immunologic function. Significant findings to date include demonstration of the following: 1) evidence of neurophysiological abnormalities in HIV+ asymptomatic patients; 2) preliminary evidence of decreased natural killer cell function precipitated by hypnotically induced anxiety; 3) confirmation of the high prevalence of alpha-delta intrusion and antidepressant responsivity in patients with fibromyalgia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00147-14 BP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Physiological Effects of Brain Peptides and Other Psychoactive Compounds

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Agu Pert, Ph.D., Chief, Unit on Behavioral Pharmacology, BPB, NIMH

Andrea Mele, BPB, NIMH; Lorna Estal, BPB, NIMH; Margaret Hamilton, BPB, NIMH; K. Wozniak, NIAAA; R. Rothman, LCS, NIMH; K.C. Rice, LMC, NIDDK; B. DeCosta, LMC, NIDDK; R.J. Weber, LMC, NIDDK; Hilleary Everist, ADAMHA; S.R.B. Weiss, BPB, NIMH; N. Ostrowski, LCM, NIMH

COOPERATING UNITS *(if any)*

BPB, CNB, LCM, LCS, NIMH; LMC, NIDDK; LCS, NIAAA; ADAMHA

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Unit on Behavioral Pharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4	3	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The striatum appears to be the most sensitive brain structure to cocaine-induced increases in extracellular dopamine (EDA). The frontal cortex was much less responsive with little evidence of a dose-dependent response. Chronic cocaine did not alter DA or DA metabolite levels in response to focal cocaine challenges. Higher DA levels were found in the striatum of cocaine pretreated rats following systemic cocaine challenges. Similar effects were found following chronic amphetamine. Autoradiographic analyses revealed that cocaine diffuses approximately 2 mm from the dialysis membrane following focal applications. GBR 12909 appeared to be effective in partially antagonizing the ability of cocaine to increase EDA. Anesthesia does not appear to alter basal EDA levels nor does it alter the peak effects of amphetamine in terms of DA release. Anesthesia does appear to potentiate the effects of morphine on EDA. Focal applications of ethanol to the striatum and n. accumbens produced a dose-dependent increase in EDA which was calcium dependent. A wide variety of structures had increased metabolic activity following a single injection of cocaine including: striatum, lateral septum, frontoparietal motor cortex, globus pallidus, substantia nigra and various pontine reticular nuclei. Decreased activity was seen in the lateral habenula and dorsomedial thalamic n. Following chronic administration increases in activity were also seen in the ventral pallidum, subthalamic n., superior calliculus and cerebellum. The most striking changes during cocaine seizures were increases in metabolic activity in the n. accumbens, olfactory n. and ventral hippocampus. All non-competitive NMDA antagonists produced profound rotational behavior in 6-OHDA lesioned rats but only TCP and PCP enhanced EDA. Increases in metabolic activity were seen only in structures receiving nigrotegmental and nigrotectal input following nigral injections of morphine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02459-01 BP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mechanism(s) of Action of Carbamazepine in the Central Nervous System of the Rat

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Mike Clark, Ph.D., Pharmacology Research Associate, BPB, NIMH

Robert M. Post, M.D., Chief, BPB
S.R.B. Weiss, Ph.D., Staff Fellow, BPB, NIMH

COOPERATING UNITS *(if any)*

Pharmacology Research Associate Program of NIGMS (Mike Clark)

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Unit on Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, MD

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5		

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The thrust of investigations by this Unit on the mechanism(s) of action of carbamazepine concentrates on two neuroactive systems which apparently have diametrically opposed physiologic functions: (1) the inhibitory adenosinergic system and (2) the excitatory glutamatergic system. During the past year, we have investigated the interactions of carbamazepine and caffeine with adenosine A-1 and A-2 receptors in an attempt to clarify the paradoxical interactions of these two drugs with the adenosine system. Additionally, we have initiated studies to explore the effects of carbamazepine and caffeine on adenosine-mediated adenylate cyclase inhibition and stimulation. Another parameter of the adenosine system currently being explored is release. Little information has been collected about adenosine release, although the synaptic levels of adenosine appear to be crucial for the resultant action of this neuromodulator. In vitro analysis of carbamazepine and caffeine effects on adenosine release have begun. In vivo analysis has been tested for feasibility and appears probable.

It is well established that adenosine inhibits the release of the excitatory amino acid glutamate. Furthermore, adenosine A-1 receptors are largely localized to the axon terminals of presumably glutamatergic neurons in the cerebellum and hippocampus (the brain areas with highest A-1 density). The role of adenosine (and the pharmacological interactions of carbamazepine and caffeine) in the regulation of extrasynaptic excitatory amino acid levels is being investigated.

The NMDA subtype of glutamate receptors is of particular interest in relation to seizures. The NMDA receptor is apparently linked to the developmental phase of kindling and long-term potentiation. We have studied the interactions of carbamazepine with NMDA receptor binding at the MK-801 site.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01833-09 BP

PERIOD COVERED

October 1, 1988 - September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Adenosine Receptors in the CNS

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Paul J. Marangos, Ph.D.   Chief, Unit on Neurochemistry

COOPERATING UNITS *(if any)*

LAB/BRANCH

Biological Psychiatry Branch

SECTION

Unit on Neurochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been incorporated into Projects Z01 MH 02459-01 BP and Z01 MH 02460-01 BP.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02432 02 CNE

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Health and Disease: Basic and Clinical Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Philip W. Gold, M.D., Chief, Clinical Neuroendocrinology Branch, NIMH

Others:	Dr. M.A. Kling	Senior Staff Fellow	CNE	NIMH
	Dr. H.J. Whitfield	Medical Staff Fellow	CNE	NIMH
	Dr. M.A. Smith	Pratt Fellow	CNE	NIMH
	Dr. T.D. Geracioti	Medical Staff Fellow	CNE	NIMH
	Dr. M.A. Demitrack	NSRA Fellow	CNE	NIMH
	Dr. H.A. Brandt	Senior Staff Fellow	SBP	NIMH

(continued on page 2)

COOPERATING UNITS *(if any)*

Developmental Endocrinology Branch, NICHD

LAB/BRANCH

SECTION

Clinical Neuroendocrinology Branch

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
22.00	17.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have attempted to elucidate pathophysiological mechanisms in the syndrome of atypical depression. This syndrome occurs across the boundaries of medical and psychiatric disorders, and is seen in patients with major depression, seasonal affective disorder, late-luteal phase mood disorder, Cushing's disease, hypothyroidism, Epstein-Barr chronic fatigue syndrome, and rheumatoid arthritis. Our data suggest that a final common pathway defect involving pathological inactivation of the CRH and locus ceruleus-norepinephrine systems confers many of the clinical and biochemical manifestations of atypical depression in each of these disorders. Moreover, our data suggest that the pathophysiological mechanisms underlying this common defect are distinct in each disorder. Hence, we are pursuing the idea that these forms of atypical depression may be analogous to the anemias, where a final common defect in overall hemoglobin synthesis and/or function contributes to many common clinical and biochemical manifestations, though the fundamental pathophysiological mechanisms differ from one subtype to another. Dr. Esther Sternberg has shown that susceptibility to arthritis in LEW/N rats reflects hypo-responsiveness of the CRH neuron to a variety of chemical and inflammatory mediators, with deficient CNS-mediated pituitary-adrenal activation leading to inadequate glucocorticoid restraint of the inflammatory response. Conversely, histocompatible F344/N rats are resistant to arthritis, owing to a hyper-responsivenss of the CRH neuron. Our data show that hypo-and hyper-responsiveness of the CRH neuron in LEW/N and F344/N rats is associated with physiological and behavioral responses to environmental stressors compatible with the putative CNS role of CRH to set into motion a set of coherent physiological and behavioral responses adaptive during threatening situations. Taken together, these data suggest that during the stress of an injury, activation of the CRH neuron serves to prevent the immune system from over-responding and to set into motion cautious behaviors to prevent exposure to further physical conflict. In this regard, human rheumatoid arthritis and the atypical depression almost invariably associated with it, may reflect an abnormality in the responsiveness of the CRH neuron. In keeping with our emphasis on elucidating mechanisms of physical and emotional stress and their relevance to major psychiatric and endocrine disorders, we have explored the effects of a variety of perturbations on the site-specific expression of genes involved in the regulation of informational substances called into play during stressful situations. Clinical studies emphasize the development, validation, and deployment of paradigms designed to study the functional integrity of stress responsive neurotransmitter systems. As an example, continuous drainage of lumbar CSF for thirty hours shows that stress-responsive neurotransmitters are secreted into the CSF in a pulsatile fashion, undergo circadian variation, and are abnormally regulated in patients with affective disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02433-02 CNE

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of Central Nervous System Functional Anatomy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Miles Herkenham	Research Psychologist	CNE, NIMH
Others:	Linda S. Brady	Senior Staff Fellow	CNE, NIMH
	John R. Glowa	Research Psychologist	CNE, NIMH
	Allison B. Lynn	Biologist	CNE, NIMH
	Evagelia Mamalaki	Fogarty Fellow	CNE, NIMH
	Eric K. Richfield	NRSA Fellow	CNE, NIMH
	Mark A. Smith	PRATT Fellow	CNE, NIMH
	Harvey J. Whitfield	Medical Staff Fellow	CNE, NIMH

COOPERATING UNITS *(if any)* Laboratory of Clinical Science, NIMH (R.B. Rothman); Laboratory of Medicinal Chemistry, NIDDK (K.C. Rice); Developmental Endocrinology Branch, NICHD (T.C. Kamilaris); Laboratory of Neurochemistry, NICHD (C.A. Bondy); Clinical Neuroscience Branch, NIMH (E. Sternberg)

LAB/BRANCH

Clinical Neuroendocrinology Branch

SECTION

Unit on Functional Neuroanatomy

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
9.0	8.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Our work can be divided into five major categories: neuroanatomy, neuropharmacology, molecular neuroendocrinology, physiology, and behavior. Mapping receptor localizations using the in vitro binding and autoradiography techniques yields important basic information about brain organization and function. We have localized the cannabinoid receptor in brain. The molecular biology group uses in situ hybridization to examine the regulation of gene expression of neuropeptides, monoamine synthesizing enzymes, and adrenal steroid receptors, which have been implicated from clinical studies in the pathophysiology of psychiatric disorders. Behavioral studies are designed to assess a variety of factors associated with anti-anxiety drug withdrawal, determinants of drug response, Maudsley rats, taste aversion learning, kindling, stress-related CNS changes, and central administration and monitoring of neuroendocrine factors in primates.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02197-03 CP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Study of the Effects of Light and Triazolam on Delayed Sleep Phase Syndrome

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	N. Rosenthal,	Chief, Unit on Outpatient Services	CPB/NIMH
Others:	J. Vanderpool	Medical Staff Fellow	CPB/NIMH
	P. Schulz	Social Worker	CPB/NIMH
	T. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
	E. Souetre	Visiting Fellow	CPB/NIMH

COOPERATING UNITS *(if any)*

Richard Allen, Ph.D., Johns Hopkins Sleep Center, Upjohn Pharmaceutical Company

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	0.5	2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Delayed sleep phase syndrome (DSPS) is characterized by a chronic inability to fall asleep in the evening and to wake up refreshed early in the morning. Patients with this condition have an abnormally delayed sleep schedule in spite of normal sleep architecture. The goal of this study was to investigate the possibility of treating DSPS by manipulating the light-dark cycle. Patients were included in the protocol on the basis of clinical screening and polysomnography. The treatment involved a crossover study between two light-dark regimens: 1) 2 weeks of bright light (full spectrum, 2500 lux) from 7:00 a.m. to 9:00 a.m. and dark goggles from 4:00 p.m. to nightfall. and 2) 2 weeks of dim light (300 lux) from 7:00 a.m. to 9:00 a.m. and clear goggles from 4:00 p.m. to nightfall.

Twenty patients completed the crossover study and expressed an overwhelming preference for the "active" over the "control" condition. This preference was corroborated by objective data, namely circadian profiles of core body temperature and multiple sleep latency studies, suggesting that rhythms had been phase-advanced to a significantly greater degree by the "active" than by the "control" condition. The results of the study add new information to the growing understanding of the importance of the light dark cycle in regulating circadian rhythms and offers a viable non-pharmacological treatment for those who suffer from DSPS.

This project has been terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02205-04 CP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Antidepressant Effects of Light in Seasonal Affective Disorder and Normal Controls

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	N. Rosenthal	Chief, Unit on Outpatient Studies	CPB/NIMH
Others:	J. Joseph-Vanderpool	Medical Staff Fellow	CPB/NIMH
	D. Oren	Medical Staff Fellow	CPB/NIMH
	P. Madden	Psychologist	CPB/NIMH
	P. Schulz	Social Worker	CPB/NIMH
	E. Sorek	Registered Nurse	CC/NURS
	C. Brown	Guest Worker	CPB/NIMH
	M. Waxler	Visiting Scientist	CPB/NIMH

COOPERATING UNITS (if any)

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL.	OTHER.
3.5	2.0	1.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We have previously shown that exposure of the eyes to bright light, but not ordinary room light can reverse the winter depressive symptoms in patients with Seasonal Affective Disorder (SAD). By now there are at least 40 controlled light treatment studies for SAD. Despite this, however, critics continue to argue that control treatments might have been implausible, which might account for the significant differences in efficacy between the active and control treatments. Since most light treatment studies performed to date have used full-spectrum light for the active condition, a novel way to re-examine the placebo issue would be to administer light of different colors. Basic science studies have shown that rod and cone photoreceptors are most sensitive to light in the green wavelength region. We therefore hypothesized that green fluorescent light would be an effective antidepressant treatment in SAD. Based on studies in animals, we hypothesized that red light would be inactive and would therefore serve as a suitable control. Previous studies by ourselves and others have shown that red light generates strong expectations of a positive outcome, which would fulfil the other parameter necessary for a good control treatment - plausibility. Additional benefits of a study in which red and green light were compared would be: 1) to help identify those photoreceptors important in the antidepressant response to light; 2) to clarify further whether ultraviolet light is necessary for its antidepressant effects. If this is not so, then this potentially toxic wavelength can be removed from the treatment without signficant loss of efficacy.

This past year we treated 14 SAD patients in a crossover study in which green and red fluorescent light, administered for two hours each morning, were compared. Green light proved to be superior to red despite equivalent *a priori* expectations of both types of light. Since the green light source contained no UV component, this finding provides additional evidence that UV light is not critical for the antidepressant effects of phototherapy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02206-05 CP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurobiology of Seasonal Affective Disorder (SAD) and Light Therapy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI.	N. Rosenthal	Chief, Unit on Outpatient Studies	CPB/NIMH
Others:	J.Joseph-Vanderpool	Medical Staff Fellow	CPB/NIMH
	D. Oren	Medical Staff Fellow	CPB/NIMH
	T. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
	P. Schulz	Social Worker	CPB/NIMH
	P. Madden	Psychologist	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	1.5	1.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Although it has been established that bright light is an effective treatment for SAD, the mechanism of its action remains unknown, as do the fundamental biological abnormalities responsible for the syndrome. In previous years we have demonstrated biological abnormalities in patients with SAD and effects of light on a wide variety of biological systems. Throughout this report I use the term "SAD" to refer only to the winter- and not the more recently described summer- variant.

This past year we have extended these studies in a number of ways. We have evaluated the hypothalamo-pituitary-adrenal (HPA) axis by measuring the ACTH and cortisol responses to infused ovine corticotrophin releasing hormone (CRH) in patients with SAD, both in untreated and light-treated conditions, and in normal controls. Like non-seasonally depressed patients, SAD patients show blunted ACTH responses to CRH, and these responses are normalized by bright light. It is unclear, though, whether this abnormality reflects an under- or overactivity of the axis.

Investigation of the visual functioning shows that patients with SAD adapt more rapidly to the dark but have normal color vision.

Since the symptoms of SAD generally remit with the advent of summer, as well as in response to light therapy, it is of great interest to compare the biological profiles of SAD patients (and normal controls) in summer and winter, and to compare the effects of summer with those of light therapy. Comparisons of SAD patients and normals in both summer and winter have shown that: 1) Both patients and normal controls have an overall lowering of body temperature in summer as compared with winter, though the effects of summer did not resemble the effects of bright light treatment. 2) Abnormally high resting metabolic rates in SAD patients were reduced to normal levels by both summer and effective light treatment. 3) M-CPP infusions showed that some behavioral responses remain abnormal even when patients are euthymic during the summer. Thus the elevated RMR seen in SAD patients appears to be a state marker of the winter depressed phase, whereas abnormal behavioral responses to m-CPP may be a trait marker for SAD.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02294-05 CP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Antidepressant Pharmacology of the Rodent Circadian System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. Duncan	Research Psychologist	CPB/NIMH
Others:	B. Gao	Fogarty Fellow	CPB/NIMH
	T. A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH

COOPERATING UNITS *(if any)*

P. Sokolove, Professor of Biological Sciences
University of Maryland, Baltimore

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.0	.75	.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have previously hypothesized that the mechanism of the antidepressant response to chronic drug therapy includes effects on the mammalian circadian system. Furthermore we have suggested that some of the undesireable effects of antidepressant drugs observed in some depressed patients are related to the effects of these drugs on the circadian clock which provides temporal organization to the daily pattern of behavior and physiology. This project focuses on the effects of antidepressant drugs on the mammalian circadian system utilizing the Syrian hamster as an animal model.

Our earlier research supports these suggestions. During the past year we have conducted research that demonstrates that inhibition of type A monoamine oxidase using clinically prescribed antidepressant medications (MAOI's) decreases the the frequency of the daily biological clock in Syrian hamsters. This observation suggests that this class of antidepressant drugs might be used to effectively treat "phase-advanced" depressive disorders. Furthermore, treatment of "phase-delayed" depressive disorders with monoamine oxidase inhibitors might induce a "delayed sleep phase syndrome" (DSPS) characterized by sleep onset insomnia. We have identified morning light as a possible treatment for MAOI-induced DSPS (see project number Z01 MH 02430-02 CP).

We have made significant progress in understanding the relationship between chronic antidepressant drug treatment, REM sleep inhibition and thermoregulation. We have observed that chronic treatment with the MAOI clorgyline decreases REM sleep and hypothalamic temperature during sleep. In contrast, peritoneal temperature is normal following chronic treatment. These results suggest that drug-induced REM sleep inhibition, which is closely associated with the antidepressant response in humans, is related to altered thermoregulation and possibly the dissociation between hypothalamic and peripheral thermoregulatory mechanisms.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02402-03 CP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Causes and Treatment of Summer Depression

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
Others:	N. E. Rosenthal	Chief, Unit on Outpatient Studies	CPB/NIMH
	J. Anderson	Guest Worker	CPB/NIMH
	H. A. Giesen	Psychologist	CPB/NIMH
	D. A. Oren	Medical Staff Fellow	CPB/NIMH
	J. R. Joseph-Vanderpool	Medical Staff Fellow	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	1	1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

There appear to be two, opposite seasonal influences on the occurrence of depression: patients are more likely to become depressed in the late spring and early summer and in the late fall and early winter than at other times of year. These seasonal patterns are of particular interest because they suggest that environmental factors can trigger and terminate affective episodes.

Considerable evidence now suggests that recurrent winter depressions are caused by light deficiency and that they can be treated with increased exposure to light. In this project we are investigating depressive symptoms and their responses to environmental manipulations in patients with recurrent summer depressions. We find that patients with summer depression are more likely than patients with winter depression to have endogenous symptoms, such as decreased appetite, decreased weight, decreased sleep, and psychomotor agitation. In contrast, patients with winter depression are more likely to have so-called atypical symptoms, such as increased appetite, carbohydrate craving, increased weight, increased sleep, and psychomotor retardation. We tested the hypothesis that seasonal changes in *light* or *temperature* might trigger summer depression by exposing remitted summer depressives in the spring to bright light (2500 lux) on one occasion and to heat (90° F) on another. Symptoms similar to summer depression were triggered by heat but not by light. Normal individuals did not exhibit significant responses to either condition. We also found that thyroid hormones decreased when patients became depressed in the summer. Currently we are measuring hormone levels in different seasons in normal subjects to determine whether the changes observed in patients were of a pathological degree. In an ongoing experiment we are investigating responses of temperature-sensitive hormones to heat and cold exposure in summer depressives and normal controls in order to determine whether differences in sensitivity exist between the two groups. We are also attempting to replicate our findings about differences in symptoms between winter and summer depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02405-03 CP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders.)*

Chemical Antidepressant Effects on Body Mass and Body Composition in Hamsters

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. Duncan	Research Psychologist	CPB/NIMH
Others:	T. A Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
.5	.25	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Antidepressant drugs are often observed to produce changes in the body mass of patients receiving treatment. Chronic treatment of Syrian hamsters with the monoamine oxidase inhibitor clorgyline prevents the normal increase in body mass as did control hamsters. The change in body mass was primarily due to an effect on body lipid content. In our earlier studies we also observed that the failure to increase body mass was not due to a decrease in caloric input since clorgyline-treated hamsters exhibited greater food intake than saline-treated hamsters. Thus, clorgyline produced a condition of negative energy balance compared to control hamsters.

We are developing a chamber that will allow online, simultaneous measurement of oxygen consumption, motor activity, food intake and body temperature. We have in the past year evaluated the performance of this system, and based on our observations, recommended that some features be re-designed in order to meet more stringent guidelines for animal care. These recommendations have been incorporated and studies are currently in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02424-02 CP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders.)*

Biological Mechanisms of the Antidepressant Effects of Sleep Deprivation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name title, laboratory, and institute affiliation)*

PI:	T. A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
Others:	N. E. Rosenthal	Chief, Unit on Outpatient Studies	CPB/NIMH
	J.R. Joseph-Vanderpool	Medical Staff Fellow	CPB/NIMH
	D. Oren	Medical Staff Fellow	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS.	PROFESSIONAL.	OTHER.
2	1	1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Total sleep deprivation for one night induces temporary remissions in sixty percent of patients with major depression; it can also induce mania in bipolar patients. Furthermore, as little as two hours of sleep can trigger depression in patients who have improved after sleep deprivation. Thus sleep appears to have a depressant effect and wakefulness a mood-elevating effect. These observations have practical implications for the management of affective illness. For example, some patients' depressions can be treated with sleep deprivation, and sleep disruption is sometimes an identifiable and preventable cause of mania. The purpose of this project is to attempt to identify biological mechanisms of the antidepressant effects of sleep deprivation. Our approach has been 1) to determine those aspects of the sleep deprivation procedure which are responsible for its antidepressant effects, and 2) to investigate the effects of sleep deprivation on biological variables, such as hormones and body temperature, which might mediate its antidepressant effects.

We have already determined 1) that exposure to light at night is not necessary for the antidepressant effects of the procedure, 2) that partial sleep deprivation in the second half of the night is more effective than partial sleep deprivation in the first half of the night, and that 3) thyroid stimulating hormone (TSH) is decreased in depression and is stimulated (normalized) by sleep deprivation.

Our current investigations of mechanisms are guided by our observation that many of the physiological responses to sleep resemble responses to heat exposure. Like heat exposure, sleep onset stimulates secretion of sweat, prolactin (PRL) and growth hormone (GH), and it inhibits metabolic heat production and secretion of TSH and triiodothyronine (T3). Like cold exposure, sleep deprivation has opposite effects. We are testing the hypothesis that the heat-like property of sleep and the cold-like property of sleep deprivation are responsible for their clinical and neuroendocrine effects. According to this hypothesis sleep deprivation in a warm environment, in contrast to a cool environment, should attenuate the antidepressant and neuroendocrine effects of sleep deprivation. Patients and normal individuals are sleep deprived on one occasion in an ambient temperature of 90° F, and on another occasion in an ambient temperature of 62° F. In six patients studied so far, the results are consistent with the predictions based on our hypothesis, but several additional subjects are needed to permit statistical evaluation of the results.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02425-02 CP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders.)*
Thermoregulatory Functions of Slow-Wave Sleep and REM Sleep

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
Others:	J.R. Joseph-Vanderpool	Medical Staff Fellow	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION
Section on Sleep Studies

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL.	OTHER.
2	1	1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
 ☐ (a1) Minors
 ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is designed to investigate basic biological functions of sleep and sleep stages. Sleep, like torpor, may serve to conserve energy by inhibiting behavioral responses to environmental stimuli and by lowering the regulated level of body temperature and metabolism. Such repeated small savings in energy expenditure could enhance an animal's chance of survival in environments with marginal energy resources. Most investigators have focused on energy conserving aspects of slow wave sleep, which appears to be associated with a temperature-lowering mechanism.

Current dogma is that thermoregulation is suspended during REM sleep. However, considerable energy is expended by the brain during REM sleep, and it seems unlikely that this expenditure serves no useful purpose. We hypothesize that REM sleep serves to generate heat locally in the brain and the eyes in order to maintain CNS temperature within acceptable limits while the rest of the body cools during sleep. Heat production is accomplished by 1) increased brain metabolism and 2) rapid eye movements. Maintenance of brain temperature may 1) facilitate rapid arousal from sleep and/or 2) protect CNS tissue in homeotherms from functional or structural impairment during the considerable body cooling which occurs when they sleep in a natural environment.

The purpose of this project is to test the hypothesis that REM sleep maintains brain temperature during body cooling by testing the response of REM sleep generating mechanisms to thermal challenges administered to the sleeping brain. Ten normal individuals participated in an experiment in which their forehead was heated on one occasion and cooled on another occasion during an entire night's sleep, while sleep EEG and rectal, tympanic, eyelid, forehead and trunk skin temperatures were continuously monitored. Heating and cooling raised and lowered, respectively, forehead and eyelid temperatures, as expected. Somewhat surprisingly, both heating and cooling lowered tympanic and rectal temperatures as the night's sleep progressed. The frequency of sleep spindles was much lower in the cooling than in the warming condition. Other sleep EEG results are still being analyzed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02426-02 CP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders.)*

Physiology of Sleep and Sleep Loss

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)*

PI:	C. Everson	Research Fellow	CPB/NIMH
Others:	T. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

Section on Sleep Studies

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	1.2	.75

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type Do not exceed the space provided.)*

The function of sleep may be one of our greatest unsolved biological mysteries. We do not know what sleep accomplishes that cannot be accomplished during wakefulness or rest. The biological significance of sleep permeates most aspects of life, from essential survival factors to higher order functions such as performance and mental well-being. Our working assumption is that outcomes of sleep loss in animals and man are traceable to the disruption of some common and basic biological mechanism. In the Sleep Physiology Laboratory, we are working to determine the physiological system(s) that may be the primary beneficiary of sleep activity. The significance of this work is in its contribution to basic biological knowledge and its ability to elucidate the role of sleep in health and disease.

Particularly compelling is the manner in which changes in sleep, energy expenditure, and thermoregulation can covary so robustly as to imply a causation, and perhaps a functional dependency. Study 1 evaluates whether a causal direction exists between hypothermia, protein malnutrition, and high rates of energy expenditure in sleep deprived rats, and how symptom development is mediated. We will work to broaden our understanding of the metabolic consequences of sleep and sleep loss by profiling brain metabolism and neurochemistry (Study 2). In Study 3, we are measuring the effect of altered energy balance on *ad libitum* sleep to assess whether normal energy balance is integral to normal sleep.

The sleep-thermoregulation-energy balance studies described in this report are the first in a series of long-term investigations. These studies are at various levels of development and methodological completeness. Accomplishments this year include the establishment of the infrastructure of the laboratory required to undertake this research; the design of a multi-variable data acquisition system; implementation of diverse methodology for measuring physiological variables; the refurbishing and modification of existing equipment; fabrication of specialized research components; and training of support personnel. *In vivo* aspects of most of the studies are currently in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02427-02 CP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders.)*

Circadian Regulation of Intergeniculate Leaflet Neuropeptide Y Messenger RNA in Syrian Hamsters

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title laboratory, and institute affiliation)*

PI:	W. C. Duncan	Research Psychologist	CPB/NIMH
Others:	E. Sutin	Biologist	CPB/NIMH
	D. Jacobowitz	Chief, Section on Histochem	LCS/NIMH
	T.A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.25	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

There are two major visual inputs to the central circadian pacemaker of mammals: a direct pathway from the retina to the pacemaker and an indirect pathway which passes through the lateral geniculate nuclei. This research project concerns the indirect visual tract or geniculohypothalamic tract (GHT) which projects to the central clock located in the hypothalamus.

The GHT conveys information pertaining to the level of ambient illumination to the central clock. This information is first transmitted through the optic tract to the intergeniculate leaflet (IGL) of the lateral geniculate nucleus. Neuropeptide Y (NPY) cell bodies are located within the IGL. These NPY cell bodies project fibers to the clock located in the suprachiasmatic nucleus of the hypothalamus. Very little is known regarding those factors that regulate NPYsynthesis within cell bodies of the IGL. We have begun to investigate the circadian and light regulation of NPY mRNA synthesis within the GHT.

Using in situ hybridization histochemical techniques, other investigators have recently demonstrated the presence of mRNA encoding for NPY in rat arcuate nuclei and cortex. Using these techniques last year we identified NPY mRNA in the vicinity of the IGL cells of Syrian hamsters. During the past year we have demonstrated using two analytical techniques a circadian variation in NPY mRNA within cells of the IGL. Preliminary data suggests that the intensity and circadian pattern of ambient lighting may control the level of mRNA encoding NPY. We anticipate comparing the pattern of NPY mRNA within the IGL with the pattern in hypothalamic nuclei that do not receive a visual projection.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02471-01 LCS

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurochemical Measures of CNS Function in Intact Animals

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: John Hsiao, PRAT Fellow, Section on Analytical Biochemistry, LCS, NIMH
Others: Sanford P. Markey, Chief, Section on Analytical Biochemistry, LCS, NIMH
Ivan N. Mefford, Chief, Unit on Clinical Neurochemistry, CPS, LCS, NIMH

COOPERATING UNITS *(if any)*

Clinical Pharmacology Section, LCS, NIMH; Surgical Neurology Branch, NINDS; Biomedical Engineering and Instrumentation Branch, DRS; LCS, NIAAA.

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Analytical Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.00	1.00	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In vivo microdialysis is a technique applicable for studying neurochemical events in intact organisms. A number of methodological advances have been made to permit chronic sampling and sampling of multiple brain regions in rats. A mathematical model for the dialysis process in vivo has been developed and validated. Its predictions impose important limitations on the interpretation and use of in vivo microdialysis, as well as permitting actual quantification of processes in brain extracellular fluid. Mapping of regional monoamine and metabolite concentrations in rat brain extracellular fluid has been performed. High concentrations of metabolites and very low concentrations of monoamine neurotransmitters suggest that there is considerable segregation of synapse and extracellular space. Studies in hemiparkinsonian monkeys demonstrate marked differences between lesioned and unlesioned sides in dopamine metabolites and alterations after transplantation. The in vivo recovery of neuropeptides and cyclic AMP has been determined.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00397-11 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Autoimmune Aspects of Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

James S. Frazier	Staff Fellow	LCS, NIMH
David M. Jacobowitz	Chief, Histopharmacology Section	LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Histopharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, MD 20892

TOTAL MAN-YEARS: 1.3	PROFESSIONAL: 1.1	OTHER: .2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Sera from normal individuals were incubated with immunoblots of two-dimensional gels of normal human cerebral cortex. Large percentages of individuals demonstrated autoantibody reactivity against a variety of proteins found within the central nervous system. These proteins include neuron specific enolase, glial fibrillary acidic protein, serum glutamic oxaloacetic transaminase and the β subunit of the G-protein. The significance of these findings are discussed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00396-11 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

A Study of Proteins Within the CNS by Two-Dimensional Gel Electrophoresis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David M. Jacobowitz	Chief, Histopharmacology Section	LCS, NIMH
Katherine L. Olsen	Guest Researcher	LCS, NIMH
William E. Heydorn	Guest Researcher	LCS, NIMH
Jorge F. Riodriquez-Sierra	Guest Researcher	LCS, NIMH

COOPERATING UNITS *(if any)*

Department of Psychiatry, SUNY, Stony Brook, NY; Department of Anatomy, Univ. of Nebraska Medical Center, Omaha, Nebraska; Merrill-Dow Pharmaceutical Co., Cincinatti, OH

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Histopharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.3	.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The identification of interesting proteins within the CNS utilizing 2-dimensional gel electrophoresis (2DE) continues. The effect of the testicular feminization (Tfm) mutation on the concentration of specific proteins in the medial preoptic area (MPO), ventromedial hypothalamus (VMH) and parietal cortex (CX) was examined. Adult Tfm and Swiss-Webster male mice were decapitated, the brains were removed and sectioned. Proteins from the three microdissected areas were separated by two-dimensional gel electrophoresis. Gels were stained with silver and then analyzed by quantitative computerized scanning densitometry. Of the 195 proteins quantified, the Tfm mutation significantly influenced the concentration of 16 proteins measured from gels of MPO tissue, 21 from VMH gels and 11 from Cx. Of these, three proteins were affected in all brain regions; and three additional proteins were shown to vary in both MPO and VMH. One protein higher in the MPO and VMH of Tfm mice was identified as the glial fibrillary acidic protein. It is suggested that the proteins influenced by the Tfm mutation are regulated by steroids, most likely androgens. Thus, these proteins may prove to be important in hormone-regulated physiological and behavioral functions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00388-13 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Coexistence of Peptides and Neurotransmitters

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David M. Jacobowitz	Chief, Histopharmacology Section	LCS, NIMH
Ellen L. Sutin	Guest Worker	LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH Laboratory of Clinical Science

SECTION Histopharmacology

INSTITUTE AND LOCATION NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS: 1.6	PROFESSIONAL: 1.2	OTHER: .4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
 ☐ (a1) Minors
 ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In situ hybridization histochemical techniques in combination with immunocytochemistry and acetylcholinesterase (AChE) histochemistry were used to study the co-localization of messenger RNA (mRNA) encoding for the neuropeptide substance P (SP) in cholinergic cells of the laterodorsal tegmental nucleus (LDT) of the rat pontine brain stem. To demonstrate that SP is synthesized within cholinergic perikarya, alternate serial sections were hybridized with 33-base, ^{35}S-labeled synthetic oligonucleotide probe encoding for SP using in situ hybridization histochemistry and processed either histochemically for AChE, or immunocytochemically for choline acetyltransferase (ChAT). In addition, serial section analysis was used to demonstrate the correlation between SP neuropeptide and SP mRNA in the same cells of LDT. These studies definitively reveal that the cholinergic neurons of the LDT contain the genetic message to synthesize SP.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00382-15 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Localization and Characterization of Brain Neuropeptides

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David M. Jacobowitz	Chief, Histopharmacology Section	LCS, NIMH
Lois Winsky	IRTA Fellow	CNB, NINCDS
Brian Martin	Visiting Scientist	NSB, NIMH

COOPERATING UNITS *(if any)*
Clinical Neuroscience Branch, Section on Molecular Pharmacology, NIMH, ADAMHA, Bethesda, Maryland 20892

LAB/BRANCH
Laboratory of Clinical Science

SECTION
Histopharmacology

INSTITUTE AND LOCATION
NIMH, ADAMHA, Bethesda, Maryland 208092

TOTAL MAN-YEARS: 3.4	PROFESSIONAL: 2.4	OTHER: 1.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A protein (MW = 29 kD, pI = 5.3) previously found to be highly localized in the cochlear nucleus of rats, rabbits and guinea pigs was purified to homogeneity from guinea pig brain. This protein (#10) bound radiolabelled calcium on electroblots and amino acid sequence of proteolytic fragments of protein 10 revealed an 82% sequence homology with a protein (calretinin) produced by a cDNA clone in chick retina. Antisera raised against protein 10 in rabbits revealed an interesting pattern of immunoreactivity within several sensory regions of rat and guinea pig brain, e.g., cochlear nuclei, vestibular nucleus, superior colliculus, olfactory bulb, as well as in retina, taste buds of the tongue and sensory ganglia (trigeminal, nodose, spiral). Other regions labelled by protein 10 antibody included, for example, cell bodies and fibers in substantia nigra (pars compacta), cerebral cortex, cerebellum, habenula and interpeduncular nucleus. Specific antibody label was tested and confirmed for bovine, monkey and human cerebral cortex. No specific antibody label was seen in any of several peripheral tissues tested in rat.

Other Collaborative Professional Personnel Engaged in the Project:

B. J. Leach	Adj. Assoc. Prof.	Dept. Anat/Cell Biol.	Georgetown Univ.

Project Description:

Objectives: For the study of function of a particular brain structure, it may be helpful to choose an animal in which the structure is either poorly developed or highly developed. The present project is partly influenced by that realization. In earlier studies we obtained evidence that in addition to its known role in maternal behavior, the thalamocingulate division of the limbic system is implicated in audiovocal communication used in maintaining maternal-offspring contact and contact of members of an affiliated group (Z01 MH 00787-08 LCS), and in play (Z01 MH 00870-03 LBEB). These three mentioned forms of behavior characterize the evolutionary transition from reptiles to mammals. Hence, it would appear a striking correlation that there is no evident counterpart of the thalamocingulate division in the reptilian brain. Cingulate, meaning girdle, refers to the convolution that "engirdles" the corpus callosum. The cingulate mesocortex (transitional cortex) falls into 4 main areas referred to as infralimbic, anterior limbic, cingular, and retrosplenial. At present, the retrosplenial area has become of particular interest because in another ongoing project (see Z01 MH 00796-04 LCS) it was found to be a source of afferents to the rostral cingulate cortex that we found to be requisite for the spontaneous production of the separation cry, a basic mammalian vocalization. One of our projects in 1967 (Number M-NP-LY-31) revealed that units in the retrosplenial area respond to photic stimulation, suggesting a role in visual functions.

Primates are believed to have stemmed from one of the insectivores, a mammalian order to which shrews, moles, and hedgehogs belong. Fossil evidence indicates that the skeletal features of some extant small insectivores are similar to primitive mammals which, in turn, are traced to the mammal-like reptiles. In 1912 M. Rose reported that in such visually deficient animals such as the shrew and mole, the granular retrosplenial area is small and poorly differentiated. The European common mole (Talpa europaea) illustrated by Rose is said to be similar to the American common mole Scalopus aquaticus. Hence for comparative purposes and possible behavioral studies, we have taken advantage of the availability of a perfused specimen to prepare serial sections of the brain.

Major Findings: The eyes of our specimen conform to published descriptions, being so small that they are difficult to find and covered by fused eyelids. The size and form of the brain are similar to that of the European mole. The location and histological appearance of the granular retrosplenial area in the American mole appears to conform in every way to that described and illustrated by Rose. In an anterior-posterior direction, it extends a distance of less than 3 mm and unlike that in most animals, does not extend up the vertical medial wall. Compared with the 12 species described in the

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH-02482-01 LCS

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Comparative Cytoarchitecture of the Cingulate Cortex

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: P.D. MacLean Intramural Research Scientist LCS, NIMH

COOPERATING UNITS *(if any)*

Department of Anatomy and Cell Biology, Georgetown University School of Medicine, Washington, D.C.

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIHAC, Poolesville, Maryland 20837

TOTAL MAN-YEARS: 1.2	PROFESSIONAL: 0.7	OTHER: 0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The transitional cingulate cortex of the limbic system has been shown to be implicated in three forms of behavior that characterize the evolutionary transition from reptiles to mammals. The comparative studies of the present project are being conducted, in part, for the purpose of selecting animals that might be useful in elucidating behavioral functions of respective cortical areas of the cingulate gyrus. The focus of the current report is the common mole that belongs to the mammalian order of insectivores with features believed to link them with the mammal-like reptiles, on the one hand, and the order of primates, on the other. Our findings show that the common American mole (Scalopus aquaticus) proves to be like the European mole (Talpa europaea) in having a small and poorly differentiated retrosplenial granular area. Hence, behavioral studies on Scalopus might be useful in revealing negative manifestations that would provide inferences about the functions of this cortex in animals in which it is well-developed. Our studies in squirrel monkeys have shown that the posterior cingulate and retrosplenial areas project to a strip of rostral cingulate cortex that is essential for the spontaneous production of the separation cry, a basic mammalian vocalization. Our prior work had also shown that photic activation of retrosplenial cells in the monkey indicate some as yet undisclosed visual function.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 02219-06 LCS

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Animal Models of Anxiety

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T.R. Insel	Staff Physician	LCS, NIMH
	J.T. Winslow	NRSA Fellow	LCS, NIMH

COOPERATING UNITS *(if any)*

Addiction Research Center, NIDA, Baltimore, MD; Laboratory of Reproductive Biology, Harvard Medical School, Boston, MA

LAB/BRANCH

Laboratory of Clinical Science, NIMH

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In the sixth year of this project, we continued our focus on developmental aspects of fear in rodent pups. Previously, we studied the role of opiate, benzodiazepine, and corticotropin-releasing factor neural systems in the modulation of the rat pup's response to social isolation. In this past year we have focused on the role of serotonin in regulating a key aspect of the behavioral response to social separation--the ultrasonic isolation call. Our interest in this system was generated by clinical studies indicating the importance of changes in serotonergic function for the mediation of anxiolytic and anti-obsessional drug effects. In the rat pup, serotonin uptake inhibitors reduced ultrasonic isolation calls while noradrenergic uptake inhibitors increased these calls. The serotonin neurotoxin methylenedioxymethamphetamine (MDMA or "Ecstasy") was also studied. In one set of experiments, we demonstrated that this "designer drug" is a selective neurotoxin with potent behavioral effects in rhesus monkeys. In studies in rat pups, we found long-term neurotoxic effects following postnatal but not prenatal administration. The loss of serotonin terminals in rat pups treated with MDMA was associated with a reduction in ultrasonic isolation calls--providing additional evidence for the importance of serotonin in mediating this form of distress behavior.

In another set of experiments, we continued to look for long-term consequences of stress in development. Although postnatal stress was not associated with long-term changes in opiate or benzodiazepine receptors, prenatal stress resulted in a decrease in mu opiate receptors in striatum and an increase in benzodiazepine receptors in the dentate gyrus in adulthood. Further studies of long-term effects of stress in development on brain serotonin receptors are planned.

Finally, during this year, our studies of receptor ontogeny in the rat brain were extended to the excitatory amino acid receptor subtypes to explore the possibility that these receptors might mediate certain aspects of developmental plasticity.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00800-02 LCS

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

A Book on Brain Evolution in Relation to Paleocerebral Functions

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P. D. MacLean	Intramural Research Scientist	LCS, NIMH
Other:			

COOPERATING UNITS *(if any)*

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Laboratory of Clinical Science

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has involved the writing and publication of a book entitled THE TRIUNE BRAIN IN EVOLUTION. Role in Paleocerebral Functions. The purpose of the book and the contents of the completed manuscript were summarized in last year's report. This year's efforts have been largely devoted to the time consuming mechanics of the book's production. The book will be about 700 pages in length, including 157 illustrations and more than 1,500 references. It is scheduled to appear in November.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
ZO1 MH 00799-03 LCS

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies on Postnatal Neuronogenesis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B.B. Stanfield	Special Expert	LCS, NIMH
Others:	T.R. Insel	Staff Physician	LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Clinical Science, NIMH

SECTION
Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION
NIMH, NIHAC, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.70	0.35	0.35

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

These neuroanatomical studies utilize ^{3}H-thymidine autoradiography and cell counting methods to study neuronogenesis in the adult dentate gyrus. We have found that the dentate granule cells which are generated in adult rats can extend axons through an apparently mature neuropil, and for appreciable distances. To determine if new neurons are added to the adult primate brain, we are studying neuronogenesis in the dentate gyrus of pygmy marmosets.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 00798-03 LCS

PERIOD COVERED
October 31, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies on the Development of the Cerebral Cortex

PRINCIPAL INVESTIGATOR *(List other professional personnal below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: B. B. Stanfield Special Expert LCS NIMH

COOPERATING UNITS *(if any)*

Washington University School of Medicine, St. Louis, MO

LAB/BRANCH
Laboratory of Clinical Science, NIMH

SECTION
Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION
NIMH, NIHAC, Poolesville, Maryland 20837

TOTAL MAN-YEARS: 1.3	PROFESSIONAL: 0.65	OTHER: 0.65

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This work focuses on the role played by certain eliminatory events which occur during the normal development of the cerebral cortex. We have utilized neuroanatomical techniques to study these events and much of our effort has concentrated on the transient visual cortical pyramidal tract which we previously identified. We have also studied the collateral elimination which occurs during the development of the projections of the locus coeruleus.

Experiments involving heterotopic cortical transplants have allowed us to identify position within the tangential plane of the cortex as a critical factor in determining which of the initially extended projections, a cortical neuron will maintain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER ZO1 MH 00797-04 LCS

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neurobiology of Attachment

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	T.R. Insel	Staff Physician	LCS, NIMH
	A.E. Johnson	Staff Fellow	LCS, NIMH
	L.E. Shapiro	Staff Fellow	LCS, NIMH

COOPERATING UNITS *(if any)*

Department of Neuroendocrinology, Rockefeller University, New York, NY; Department of Psychology, Boston College, Boston, MA

LAB/BRANCH
Laboratory of Clinical Science, NIMH

SECTION
Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION
NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.0	1.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In the first three years of this project, we studied the role of oxytocin in mediating maternal behavior using several new neurobiologic techniques. On the basis of these various studies, we concluded that oxytocin receptors increase in a regionally specific fashion with the onset of maternal behavior. In addition, we found that the physiologic changes in gonadal steroids accompanying parturition are sufficient for this change in oxytocin receptors. It has long been known that gonadal steroids are important for the expression of maternal behavior--our finding that steroids alter a key neuropeptide receptor system suggested a novel mechanism for estrogen, progesterone, or androgens to regulate behavior. Much of this past year focused on the nature of the gonadal steroid--oxytocin receptor interaction and ultimately the mechanisms of gonadal steroid actions in the rat brain. We compared various steroid treatment regimens, delineated the time course for the effects, demonstrated responses to physiologic changes in steroids, and defined the regional specificity. The ontogeny of oxytocin receptors demonstrated that regions dependent on gonadal steroids only express receptors after puberty. All of these studies were based on a new oxytocin analogue, ^{125}I-OVTA (or Compound 6) which we characterized during the past year. We have also investigated the functional consequences of this steroid-oxytocin receptor interaction. We investigated the possibility that progesterone coupled the oxytocin receptor to the phosphoinositol hydrolysis cycle. In a recent set of experiments, we demonstrated that estrogen increased expression of the c-fos proto-oncogene product in regions of the brain known to be important for maternal and reproductive behavior.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00796-04 LCS

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cytochemical Tracing of Thalamic Connections with Midline Frontal Cortex

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: P. D. MacLean Intramural Research Scientist LCS, NIMH

Other:

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS: 0.6	PROFESSIONAL: 0.4	OTHER: 0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This report is the last of a project that has used cytochemical tracing techniques toward clarifying the brainstem and other connections of midline frontal cortex implicated in the spontaneous production of the separation cry (isolation call), a basic mammalian vocalization. The final phase has been concerned with completing exploration of the midline cortex and an attempt to clarify anatomically how cerebellar mechanisms are brought into play. Some additional findings are described in regard to a spotty network of midline pontine cells that project to midline frontal areas.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00433-09 LCS

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Role of Neuropeptides in Neuroendocrine Regulation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.M. Saavedra, M.D.	Medical Officer	SP LCS NIMH
Others:	E. Castren	Visiting Fellow	SP LCS NIMH
	A. Himeno	Visiting Fellow	SP LCS NIMH
	M. Kurihara	Visiting Fellow	SP LCS NIMH
	J.T. Laitinen	Visiting Fellow	SP LCS NIMH
	J.E.B. Pinto	Visiting Scientist	SP LCS NIMH
	T. Torda	Visiting Associate	SP LCS NIMH
	T. Agui	Visiting Fellow	SP LCS NIMH

COOPERATING UNITS *(if any)*

Experimental Therapeutics Branch, NINCDS; Lawrence Berkeley Laboratory, UC, Berkeley, CA; Dept Med. Chem., Purdue University, IN; Dept. Physiol., University of Oulu, Finland

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
6.5	6.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We characterized receptors for the psychotomimetic dimethoxyphenylisopropylamine (DOI) in individual brain nuclei. Chronic administration of this hallucinogenic compound to rats downregulated both agonist and antagonist 5-HT_2 binding in cortex. DOI receptors were characterized in human platelets, by newly developed autoradiographic methods with greatly increased sensitivity.

We found a diurnal rhythm of melatonin binding affinity in the rat suprachiasmatic nucleus, the biological clock, and that cholinergic receptors stimulate phosphoinositide hydrolysis in the pineal gland.

We characterized different subtypes of receptors for the heart hormone atrial natriuretic peptide (ANP), on the basis of selective displacement with ANP analogs. Receptors for a specific brain natriuretic peptide were characterized in sympathetic ganglia, adrenal gland, kidney, and brain.

We established a role for brain angiotensin receptors in the regulation of corticotrophin-releasing hormone (CRF) and in the regulation of the hypothalamic-pituitary-adrenal axis. Peripheral administration of blockers of angiotensin II formation selectively regulates the expression of angiotensin II receptors in brain.

Angiotensin II and B_2-adrenoceptors were characterized in peripheral sympathetic ganglia where they play a role in the regulation of sympathetic tone.

Other Collaborative Professional Personnel Engaged on the Project

M. Herkenham, Ph.D.	Chief, UFN	CNE	NIMH
L.S. Brady, Ph.D.	Senior Staff Fellow	CNE	NIMH
S. McLean, Ph.D.	Senior Staff Fellow	CNE	NIMH
K.C. Rice, Ph.D.	Chief, DDS	LMC	NIDDK
A.E. Jacobson, Ph.D.	Research Chemist	LMC	NIDDK
B.R. de Costa, Ph.D.	Fogarty Fellow	LMC	NIDDK
L.C. Band, Ph.D.	IRTA Fellow	LMC	NIDDK
A.A. Reid, M.S.	Technician	LMC	NIDDK

Project Descriptions

Project 1. Characterization of CNS Opioid Receptors

1A. Development of small molecules as research tools. This work, conducted in collaboration with Dr. Rice, involves the *de novo* development of new agents as well as characterization of potentially useful chemicals synthesized in other laboratories. These agents include site-directed alkylating agents, radioligands, and drugs that are selective for receptor subtypes.

Considerable effort has gone into developing site-directed acylating agents selective for the opioid κ receptor.

In one study, synthesis and evaluation of (IS,2S)-trans-2-isothiocyanato-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide (Ia), a novel κ opioid receptor specific acylating agent and its enantiomer, (IR,2R)-trans-2-isothiocyanato-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide (Ib), are described. The ability of Ia and Ib to function as irreversible inhibitors of opioid binding was tested *in vitro* by incubating brain membranes with 1 nM of each compound for 60 min at 25°C followed by a washing procedure sufficient to remove unreacted drug. Incubation of guinea pig membranes depleted of μ and δ opioid receptors with Ia followed by washing reduced the binding of the κ selective agonist, $[^3H]5\alpha, 7\alpha, 8\beta$-(-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro(4,5)dec-8-yl]-phenyl-benzeneacetamide ($[^3H]$U69,593), to 11% of control. The effect was stereoselective as Ib had no effect under these conditions. Compound Ia failed to effect the binding of $[^3H]$DADLE (δ opioid receptors) and $[^3H]$FOXY (μ opioid receptors). However, its enantiomer, Ib, although having no effect on δ binding gave a significant irreversible inhibition of μ binding. When κ receptors in guinea pig brain membranes depleted of μ and δ opioid receptors were assayed using $[^3H]$bremazocine, neither Ia nor Ib irreversibly inhibited binding. Compound Ia had an apparent IC_{50} of 52 ± 7.5 nM in "reversible" displacement of a single concentration of $[^3H]$U69,593 with varying concentrations of Ia. Pretreatment of guinea pig brain membranes with 100 nM of Ia followed by washing and Scatchard analysis of $[^3H]$U69,593 binding revealed an increase in the K_d from 4.47 ± 0.21 nM to 8.45 ± 0.41 nM without significant change in the B_{max}. A greater increase in K_d without change in B_{max} was observed on treatment of the membranes with 300 nM of Ia. The results confirm that irreversible inhibition of $[^3H]$U69,593 binding after preincubation with Ia is the result of a decrease in affinity of the κ receptors as opposed to a reduction in the total number of available receptors. Furthermore, failure of Ia to affect $[^3H]$bremazocine binding in pretreated membranes is further evidence for heterogeneity of κ opioid receptors.

Unfortunately, (IS,2S)-trans-2-isothiocyanato-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide did not acylate κ receptors when administered icv. Therefore, the isothiocyanate analog, (1S,2S)-trans-2-isothiocyanato-4,5-dichloro-N-methyl-N-[2-(

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02429-02 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Characterization of CNS Opioid Receptors and Psychotomimetic Binding Sites

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Richard B. Rothman, M.D., Ph.D., Chief, Unit on Receptor Studies, LCS, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Medicinal Chemistry, NIDDK; Walter Reed Army Inst. Res., Washington, DC; Unit on Functional Neuroanatomy, CNE, NIMH

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION

National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	1.5	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A major focus of work is the study of CNS opioid receptors. A goal of this work is to define additional opioid receptor subtypes and develop new small molecules as research tools. Site-directed acylating agents selective for the κ type of opioid receptor were developed, including UPHIT, which is active when administered intracerebroventricularly. Several studies demonstrated the existence of multiple subtypes of κ receptors, one of which may be associated with psychotic behavior in humans. Using the site-directed alkylating agent, β-funaltrexamine, we obtained data demonstrating that this irreversible ligand selectively alkylates the opioid receptor complex, and prevents the modulatory effects of δ receptor ligands on morphine antinociception. Studies of morphine tolerance demonstrated that chronic morphine administration selectively upregulated a subtype of μ binding site, and the receptor upregulation was visualized using quantitative autoradiography. Alterations in the stereochemistry of the κ selective agonist, U50,488, resulted in ligands selective for the σ receptor, a putative psychotomimetic binding site.

PHS 6040 (Rev. 1/84) GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 MH 00339-08 LCS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neuropharmacology of Cognition and Mood in Geriatric Neuropsychiatry

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Trey Sunderland, M.D., Chief, Unit on Geriatric Psychopharmacology, LCS, NIMH

COOPERATING UNITS *(if any)*
Laboratory of Cerebral Metabolism, NIMH; Biological Psychiatry Branch, NIMH;
Medical Neurology Branch, NINDS

LAB/BRANCH
Laboratory of Clinical Science

SECTION
Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION
National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
6	3.5	3.0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The pharmacologic challenge model continues to be at the center of most studies within the Unit on Geriatric Psychopharmacology. By using drugs to investigate underlying biologic function, we are testing potential diagnostic methods, while simultaneously attempting to develop new drug treatments. This past year, we concluded several major studies of Alzheimer's disease patients using novel pharmacological agents, such as m-chlorophenylpiperazine (m-CPP) and thyrotropin-releasing hormone (TRH). While Alzheimer's disease is best known for its cholinergic neuropathology, there are deficits in many other neurotransmitter systems. Our acute studies with the serotonin agonist, m-CPP, and the neuropeptide, TRH, have revealed potential benefits for both of these approaches and have opened the way for future combination strategies in Alzheimer's disease therapy. In addition, we have extended our earlier work with the monoamine oxidase inhibitor, L-deprenyl, to include a long-term study of its effects on the course of Alzheimer's disease.

With the high degree of overlapping symptoms between geriatric depression and dementia, it is essential to clinically evaluate patients carefully. Consequently, we have systematically compared and contrasted these two major geriatric disorders to ensure better diagnostic accuracy and to understand the common pathologic mechanisms. Given the lack of definitive diagnostic markers, we developed special rating scales to measure depression [i.e., Dementia Mood Assessment Scale (DMAS)] and daily functioning in dementia subjects [i.e., Daily Activities Questionnaire (DAQ)]. Biological specimens such as cerebrospinal fluid have also been tested to help differentiate depressed and demented patients from age-matched controls. In addition, extensive clinical and experimental cognitive testing provides us with important profiling tools to evaluate better our patients. Together, these instruments allow us to assess the effectiveness of our ongoing medication studies and will enable us to continue our correlative and longitudinal studies in the future.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00337-10 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuropharmacology of Neuroendocrine and Neurotransmitter Regulatory Mechanisms

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dennis L. Murphy, M.D., Chief, Laboratory of Clinical Science, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION

National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892

TOTAL MAN-YEARS: 2.2	PROFESSIONAL: 1.4	OTHER: 0.8

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The functional status of the serotonin (5-HT) neurotransmitter system has been studied comparatively in humans and rhesus monkeys using 5-HT-selective agonists and antagonists as pharmacologic probes. Psychophysiologic responses, including blood pressure, neuroendocrine measures, temperature, penile erections, and subjectively assessed as well as objectively rated behavioral changes, are differentially altered by serotonin agonists in certain subgroups depending on dose and route of administration. Many other examples of differential responses support the concept that humans as well as other species have functionally different, independently modulated serotonergic subsystems which appear to correspond, at least in part, to the heterogeneous 5-HT binding sites and neuroanatomical subpathways identified *in vivo*. Other studies have begun to explore the occurrence and significance of antibodies to several peptides in plasma and cerebrospinal fluid in neuropsychiatric patients and normal controls. In a genetic study of monoamine neurotransmitter regulations, marked amine and amine metabolite changes were found in four individuals with submicroscopic X-chromosomal deletion shown to affect the genes for monoamine oxidase type A and type B.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00336-10 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Phenomenology and Treatment of Obsessive-Compulsive Disorder in Adults

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dennis L. Murphy, M.D., Chief, Laboratory of Clinical Science, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION

National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892

TOTAL MAN-YEARS: 3.5	PROFESSIONAL: 2.8	OTHER: 0.7

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Our studies conducted in the last year on obsessive-compulsive disorder (OCD) have had a primary focus on treatment of the disorder with clomipramine. Investigations conducted here and elsewhere have conclusively shown that this tricyclic drug is more effective than structurally similar tricyclics such as desipramine, imipramine, and amitriptyline. In contrast, in depression, panic disorder, and other psychiatric disorders, these agents have essentially identical efficacy. In a double-blind study attempting to evaluate what duration of clomipramine maintenance treatment might be most useful, we found that patients treated for 5 to 27 months all had a similar, very high relapse rate during placebo substitution for seven weeks. As all patients responded to clomipramine reinstatement, it appears that longer term maintenance treatment with this agent is useful. In studies evaluating possible serotonergic contributions to clomipramine's therapeutic effects, brief coadministration of the serotonin antagonist, metergoline, led to return of OC symptoms in comparison to double-blind coadministration of placebo. In a small patient sample, orbital frontal glucose metabolism examined by positron emission tomography was found to be increased in OCD patients compared to controls, a difference that diminished when patients improved after four months of clomipramine treatment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00332-11 LCS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Animal Models for the Study of Neuropharmacologic Effects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Charanjit S. Aulakh, Ph.D., Staff Fellow, Section on Clinical Neuropharmacology, LCS, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Cerebral Metabolism, National Institute of Mental Health

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION

National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.6	1.3	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Administration of 5-HT_1 receptor agonist, m-chlorophenylpiperazine (m-CPP), to rats produced dose-dependent decreases in food intake, locomotor activity, and hyperthermia, increases in plasma prolactin and corticosterone, and a decrease in plasma growth hormone. Long-term (21-23 day) treatment with the tricyclic antidepressant, imipramine, potentiated the effect of m-CPP on food intake, locomotor activity, and plasma prolactin but not corticosterone concentrations, and also attenuated m-CPP-induced hyperthermia. Long-term treatment with clomipramine (a tricyclic antidepressant as well as antiobsessive-compulsive agent) potentiated the effect of m-CPP on plasma prolactin concentrations but not on food intake or locomotor activity, and also attenuated the effect of m-CPP on temperature and plasma corticosterone concentrations. Long-term treatment with the monoamine oxidase (MAO) type A inhibiting antidepressant, clorgyline, attenuated the effect of m-CPP on food intake, locomotor activity, temperature, and plasma prolactin but not corticosterone concentrations. Long-term treatment with lithium (antimanic and antidepressant agent) attenuated the effect of m-CPP on food intake but not locomotor activity. These findings indicate that various agents effective in different types of affective disorders exert differential modulatory influences on serotonergic mechanisms regulating food intake, locomotor activity, temperature, and neuroendocrine changes *in vivo*.

In another study, administration of clorgyline to rats for 21 days caused a significant decrease in cortical [^{3}H]dihydroalprenolol binding. Selective lesioning of central serotonergic axons by 5,7-dihydroxytryptamine (5,7-DHT) or inhibition of 5-HT synthesis by parachlorophenylalanine (PCPA) caused significant 5-HT and 5-HIAA depletions in the cortex without much effect on norepinephrine and dopamine concentrations, but did not have any significant effect on ß-adrenoceptor density, and also failed to attenuate clorgyline-induced decreases in ß-adrenoceptor density. Clorgyline treatment partially antagonized 5-HT depletion by the 5,7-DHT lesion or PCPA treatment. These findings suggest that due to their ability to raise 5-HT concentrations, MAO-inhibiting antidepressants may be a better alternative than the tricyclics in treating depressed patients with reduced 5-HT if down-regulation of ß-adrenoceptors is critical for antidepressant efficacy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00277-10 LCS

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Synthesis of Stable Isotope Labeled Compounds

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: Sanford P. Markey, Chief, Section on Analytical Biochemistry, LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Analytical Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

PROJECT DISCONTINUED

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02240 036
CHP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neurobiology of Disruptive Behavior Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Judith L. Rapoport, M.D., Chief, CHP, NIMH
Markus J.P. Kruesi, M.D., Staff Psychiatrist, CHP, NIMH
William Z. Potter, M.D., Ph.D., Chief, Sect. on Clin. Pharmacol., LCS, NIMH
Markku Linnoila, M.D., Ph.D., Chief, LCS, NIAAA
Josephine Elia, M.D., Medical Staff Fellow, CHP, NIMH
Thomas Cooper, M.A., Nathan Kline Institute

COOPERATING UNITS *(if any)*
Section on Clinical Pharmacology, LCS, NIMH
National Institute on Alcohol, Abuse and Alcoholism
Section on Clinical Brain Imaging, LCM, NIMH

LAB/BRANCH
Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS: 3.33	PROFESSIONAL: 2.33	OTHER: 1.00

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Decreased concentrations of cerebrospinal fluid 5-hydroxyindoleacetic acid (CSF 5-HIAA) were found in 29 children with disruptive behavior disorders compared to 43 pediatric patients with Obsessive Compulsive Disorder. Negative correlations were found between measures of aggression and 5-HIAA concentration in the Disruptive group. Prospective study of subjective and objective side effects of lumbar punctures in children has established the safety and relative lack of discomfort with the procedure. Prospective follow-up to assess the predictive validity of CSF 5-HIAA is underway.

Pharmacologic studies aimed at clarifying stimulant drug efficacy in Disruptive Behavior Disorders continue. Amphetamine and methylphenidate, the two most frequently utilized treatments for Attention Deficit Hyperactivity Disorder (ADHD), have been contrasted clinically and biochemically in 31 children in a crossover design. Urinary and plasma monoamine changes differed for the two drugs, with only urinary epinephrine and metanephrine similarly affected. Fenfluramine, a structural analog of amphetamine, had no benefit for ADHD in 20 hyperactive boys.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 M- 00301-03

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Diagnosis in Child Psychiatry

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith L. Rapoport, M.D., Chief, CHP, NIMH
Josephine Elia, M.D., Medical Staff Fellow, CHP, NIMH
Robert Spitzer, M.D., Professor of Psychiatry, New York State Psychiatric Institute, New York, N.Y.

COOPERATING UNITS *(if any)*

The New York State Psychiatric Institute, N.Y., N.Y.

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.20	.10	.10

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The validity of several DSM-III pediatric psychiatric diagnoses remains controversial. Studies are underway across several centers addressing the validity of the diagnostic distinction between situational and cross situational hyperactivity, and between obsessive compulsive disorder (OCD), subclinical OCD, and compulsive personality disorder.

Comparison of clinical and rating scale scores for 30 hyperactive and conduct disordered children formed part of the determination of diagnostic criteria for these disorders in DSM-III-R.

The validity of the distinction between OCD, subclinical OCD, OCP and other disorders with O-C features was preliminarily assessed with: studies of interrater reliability, associated features and follow-up status of a community sample of OCD and OC "spectrum" disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00178 069
CHP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Brain Structure & Function in Developmental Neuropsych. Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith M. Rumsey, Ph.D., CHP, NIMH
Robert Cohen, M.D., Chief, Sect. on Clin. Brain Imaging, LCM, NIMH
Alan Zametkin, M.D., Sect. on Clin. Brain Imaging, LCM, NIMH
Connie Duncan, Ph.D., LPP, NIMH
Shelley Smith, M.D., Boys Town Research Center

COOPERATING UNITS *(if any)*

Clinical Brain Disorders Branch, NIMH; Sect. on Clin. Brain Imaging, LCM, NIMH; Lab. of Psychol. & Psychopathology, NIMH; Boys Town Research Center, Omaha, Nebraska

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.0	1.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Neuropsychological studies of severely dyslexic men and high-functioning autistic men find severe phonological and general language and verbal memory deficits in dyslexia and deficits in higher-level, executive problem-solving in autism. These findings implicate left perisylvian regions in dyslexia and suggest frontal and/or subcortical dysfunction in autism.

A "pattern," or correlational, analysis of resting PET glucose metabolic data in 14 autistic men and 14 controls found unusual relationships between frontal and parietal and between frontal/parietal/subcortical regions, further implicating involvement of these neocortical/subcortical pathways in autism.

Event-related potentials of 15 severely dyslexic men showed decreased P300 amplitudes in both auditory and visual modalities in choice, but not in simple, reaction times studies, indicating deficient information processing only under cognitively demanding conditions.

Fourteen normal controls and one severely dyslexic adult male have been studied with a variety of activation tasks and in a resting state with PET using oxygen-15-labeled water as a tracer. This data

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00153-01Q3
CHP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Treatment of Obsessional Children and Adolescents with Clomipramine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Judith L. Rapoport, M.D., Chief, CHP, NIMH
Henrietta Leonard, M.D., NRSA Fellow, CHP, NIMH
Theodore Zahn, Ph.D., Research Psychologist, LPP, NIMH
Agnes Whitaker, M.D., Columbia University
Susan Swedo, M.D., Staff Fellow, CHP, NIMH
Mark Shapiro, M.D., LN, NIA
Dennis Murphy, M.D., CN, NIMH
Markus J.P. Kruesi, M.D., Staff Psychiatrist, CHP, NIMH

COOPERATING UNITS *(if any)*
Lab. of Psychol. & Psychopathology, NIMH, Clin. Neuropharmacology, Branch, NIMH; National Inst. of Neurol. & Communicative Disorders & Stroke; Columbia University, National Institute on Aging

LAB/BRANCH
Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS: 5.8	PROFESSIONAL: 4.0	OTHER: 1.8

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Obsessive Compulsive Disorder (OCD) is now recognized as a common mental disorder, occurring in perhaps four million people in this country alone. In adolescents, the prevalence may be one percent.

A double blind comparison of clomipramine (CMI) and desmethylimipramine (DMI) in forty-eight children and adolescents found CMI to be significantly superior to DMI for the treatment of severe primary OCD.

Trichotillomania (hair pulling) has been treatment with CMI in a double-blind study with nineteen patients. Again, CMI was highly effective while DMI was not.

A pilot study of nine dogs with acralick dermatitis (excessive licking of paws and body leading to ulcers and bleeding) found clomipramine effective short term treatment, while desmethylimipramine was ineffective. Canine acralick may prove to be good model for obsessive compulsive disorder.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02465-01 CNG

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Genetic Mapping Development

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E. Gershon	Chief	CNG, NIMH
Others:	W-T Hsieh	Sr. Staff Fellow	CNG, NIMH
	P. Gejman	Visiting Associate	CNG, NIMH
	S. Detera-Wadleigh	Sr. Staff Fellow	CNG, NIMH
	J. Guroff	Social Science Analyst	CNG, NIMH
	L. Goldin	Geneticist	CNG, NIMH
	M. Martinez	Visiting Fellow	CNG, NIMH
	T. Bonner	Special Expert	LCB, NIMH

COOPERATING UNITS *(if any)*
Mark Gray, Tufts University; Carol Jones, University of Colorado; Cassandra Smith, University of California at Berkeley.

LAB/BRANCH
Clinical Neurogenetics Branch

SECTION
Section on Clinical Genetics

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	2.5	1.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Improvements in linkage technology are required for systematic genomic mapping of complex diseases, such as manic-depressive illness and schizophrenia.

We are developing denaturing grandient gel electrophoresis as an alternative to RFLPs, for detection of polymorphism not present at restriction sites.

Physical mapping of regions of interest in neuropsychiatric disease: on chromosome 11p15.5, and chromosome 4pter, a series of genes is being mapped using pulsed field gel electrophoresis (PFGE). The use of infrequent cutter restriction enzymes and large fragment PFGE as part of systematic genomic mapping is being developed.

Polymerase chain reaction (PCR) gene amplification is being used to detect the various genetic species in families of homologous receptor genes.

A data management and automated linkage analysis system has been developed, for use in large scale genomic mapping of illness.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02464-01 CNG

PERIOD COVERED

October 1, 1989 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mapping of Psychiatric Disorders and Neurotransmitter-related Genes-II

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Wade Berrettini	Medical Officer	CNG, NIMH
Others:	Margaret Hoehe	Staff Fellow	CNG, NIMH
	Sevilla Detera-Wadleigh	Senior Staff Fellow	CNG, NIMH
	Pablo Gejman	Visiting Associate	CNG, NIMH
	Wang-Ting Hsieh	Senior Staff Fellow	CNG, NIMH
	Elliot Gershon	Chief	CNG, NIMH

COOPERATING UNITS *(if any)*

William Byerley, Assistant Professor, Ray White, Professor, and Marc Leppert, Assistant Professor, University of Utah, Salt Lake City, UT.

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: 4.5	PROFESSIONAL: 1.5	OTHER: 3.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Linkage of illness to the Xq28 region (colorblindness region of X chromosome) was excluded in nine bipolar (BP) pedigrees (consisting of 160 subjects, 59 affected, no male-to-male transmission), indicating that linkage of BP disease to the Xq28 region is not as common as suggested by others. Linkage was also excluded to the Factor IX locus in Xq27 for eight BP pedigrees. In three of the pedigrees, polymorphism was detected through polymerase chain reaction (PCR).

Using restriction fragment length polymorphisms discovered in our laboratory, we evaluated genes for the beta and alpha-adrenergic receptors for linkage to illness in BP pedigrees. Linkage could be excluded in each case for seven pedigrees. These genes were genetically mapped using CEPH reference pedigrees. Map locations suggest an 8-15 cM fragment containing an α_2 and a β_1 receptor gene may have been duplicated on chromosomes 5 and 10.

In addition, linkage to the phenylethanolamine-N-methyltransferase (PNMT) gene could be excluded in seven BP families.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02463-01 CNG

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mathematical Issues in Genetic Analysis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	L. R. Goldin	Research Geneticist	CNG, NIMH
Others:	M. M. Martinez	Guest Researcher	CNG, NIMH
	E. S. Gershon	Chief	CNG, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	1.8	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Power of linkage detection under heterogeneity in complex inheritance. a) Linkage can be detected in clinically feasible sample sizes of nuclear families when there is heterogeneity. Unaffected siblings can sometimes be eliminated from laboratory workup with little loss of efficiency. b) Moderate sized pedigrees are more efficient than nuclear families in detecting linkage. Selection of multiplex pedigrees favors the detection of dominant genes or recessive genes with high penetrance. The series of manic-depressive pedigrees collected in the CNG has approximately 80% power to find a linkage (1% recombination) if only 25% of families are linked.

Sample size needed for one marker locus vs. a map of two marker loci. Under many different assumptions, the distance of a disease gene to one marker locus corresponds (in sample size required to detect linkage) to the disease being approximately twice as far from either of two linked markers if the disease is midway between the two markers.

Association studies. Finding disequilibrium between a disease and linked markers can narrow the possible candidate genes for the disease. We have shown that even under conditions of genetic heterogeneity, clinically realistic sample sizes of unrelated individuals or a small number of linked pedigrees can be powerful for demonstrating disequilibrium.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH02237-05 CNG

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mapping of Psychiatric Disease and Neurotransmission Related Genes-I

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S. Detera-Wadleigh	Senior Staff Fellow	CNG, NIMH
Others:	C. de Miguel	Visiting Fellow	CNG, NIMH
	I. Encio	Visiting Fellow	CNG, NIMH
	L. Goldin	Geneticist	CNG, NIMH
	W. Berrettini	Senior Staff Psychiatrist	CNG. NIMH
	E. Gershon	Chief	CNG, NIMH
	P. Gejman	Visiting Associate	CNG. NIMH

COOPERATING UNITS *(if any)*

R. Sherrington, Post-doctoral Fellow, Middlesex Medical School, London, England
H. Gurling, Senior Researcher, Middlesex Medical School, London, England

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Mapping of Psychiatric Disease Genes: Exclusion of linkage to chromosome 11, region p15 in eight families with manic-depressive illness was obtained using polymorphic probes to HRAS1 and INS.

Exclusion of linkage to chromosome 5, region q11-13 in five families with schizophrenia was obtained by multipoint analysis using probes to the loci D5S39, D5S76, and DHFR.

A systematic mapping of the human genome to find a linkage region for manic-depressive illness has been initiated using 13 medium to large sized pedigrees, as part of a 20 pedigree project. The initial step is the construction of a manic-depressive illness map of the chromosome 5q region.

Fine Mapping of the Glucocorticoid Receptor Gene (GRL) Region: Human genomic clones spanning approximately 200 kb of the GRL region have been isolated, aligned, mapped and the exon-intron arrangement characterized.

Molecular Cloning of a cDNA for a Novel Protein Kinase from Rat Brain: A cDNA clone from rat brain cDNA library containing consensus domains for a serine/threonine kinase and consensus phosphorylation sites was isolated and sequenced. The protein is homologous to human and yeast cell division control proteins. Genomic blot pattern suggests that it is encoded by a single gene.

Mapping of Human Calmodulin Genes and Characterization of a Pseudogene: An intronless calmodulin pseudogene localized on chromosome 17 was isolated and sequenced. Using probes from various segments of a human cDNA which we have previously isolated, calmodulin was mapped to five different chromosomes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 MH 00086-14 CNG

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Outpatient Clinic for Genetic and Pharmacologic Studies of Affective Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Wade H. Berrettini	Medical Officer	CNG, NIMH
Others:	Elliot S. Gershon	Chief	CNG, NIMH
	Susan Simmons-Alling	Clinical Nurse Expert	CC, NIH
	Mary E. Maxwell	Res. Social Worker	CNG, NIMH
	Ann L. Smith	Res. Social Worker	CNG, NIMH
	David Rubinow	Clinical Director	IRP, NIMH

COOPERATING UNITS *(if any)*
J. Nurnberger, Professor, Indiana Univ.; B. Byerley, Asst. Professor, Univ. of Utah; W. Kaye, Assoc. Professor, Univ. of Pittsburgh, PA.; M. Lesem, Assist. Professor, Univ. of TX; J. Leckman, Assoc. Professor, Yale Univ. Boston, MA.

LAB/BRANCH
Clinical Neurogenetics Branch

SECTION
Section of Clinical Neurogenetics

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	1.0	4.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Recruitment and investigation of moderate-size bipolar families for molecular genetic studies on the inheritance of this illness have continued. Twenty-six families have been identified, consisting of 420 subjects, of whom 200 are affected. Lymphoblastoid cell lines have been established for more than 300 of these subjects. These cell lines will be used to screen the genome with evenly spaced DNA probes in a search for linkage. Mathematical simulations based on a 20% pedigree series indicate that it has 80% power to detect linkage (at 1% recombination) when 25% of these families are linked to the locus in question. Thus, this series of pedigrees can be used to detect common genetic causes of bipolar disease. Ten schizophrenic pedigrees have been identified, consisting of 190 subjects, 61 of whom are affected (schizoaffective or schizophrenic diagnoses). Lymphoblastoid cell lines have been established on 135 of these subjects.

A family study of bulimia has yielded evidence for the familial association of bulimia with major affective disorder, substance abuse and antisocial personality.

We have determined that an acute intravenous infusion of physostigmine increases CSF neuropeptide Y in both man and non-human primates. CSF galanin and vasoactive intestinal peptide are lower in subjects with progressive supranuclear palsy (PSP), compared to subjects with Alzheimer's disease (AD) or age-matched controls.

A longitudinal prospective study of adolescents at high risk for affective disorder has been continued. These offspring of bipolar parents are being followed to determine whether predictors of illness can be identified.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00084-15 CNG

PERIOD COVERED

October 1, 1988 to September 30, 1898

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Genetic-Biologic Studies of Psychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	E. Gershon,	Chief	CNG, NIMH
Others:	W. Berrettini	Staff Physician	CNG, NIMH
	J. Hamovit	Resarch Social Worker	CNG, NIMH
	J. Guroff	Social Science Analyst	CNG, NIMH
	D. Kazuba	Psychologist	CNG, NIMH

COOPERATING UNITS *(if any)*

L. DeLisi, Assistant Professor, SUNY, Stoneybrook, NY; J. Nurnberger, Professor, Indiana Univ. Medical Ctr., Indiana, IN.

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.0	0.0	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is terminated as of this year with its components distributed into Z01 MH 02463-01 CNG entitled, "Mathmatical Issues in Genetic Analysis" and Z01 MH 00086-12 entitled, "Outpatient Clinic for Genetic and Pharmacologic Studies of Affective Disorders".

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02346-02 NS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Immunology of Schizophrenia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: M.H. Rapaport, Senior Staff Fellow, NSB, DIRP, NIMH

Others:	D. Pickar	Acting Chief	NS, NIMH
	S. Paul	Chief, Sec on Mol Pharmacol	NS, NIMH
	C. McAllister	Staff Fellow	NS, NIMH

COOPERATING UNITS (if any)

Section on Molecular Pharmacology, NSB, NIMH, and Laboratory of Developmental Neurobiology, NICHHD

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	1.75	.25

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project studies the immunology of schizophrenia and encompasses three lines of investigation: 1) studies of possible autoimmune and infectious etiologies of schizophrenia (including studies of cerebral spinal fluid for antibodies, lymphocytes), 2) studies of cytotoxic factors, and 3) studies of the in vivo effects of antipsychotic agents on immune function. One major study is the investigation of genotypic and phenotypic markers of peripheral lymphocytes. In particular, we are simultaneously evaluating markers of T and B lymphocytes and HLA haplotypes in selected patients. Preliminary evidence indicates that approximately 30% of schizophrenic patients have elevated numbers of CD5-positive B lymphocytes in their peripheral blood. This finding is similar to that reported for rheumatoid arthritis and Sjogrens syndrome. During the past year, we expanded the studies of autoimmune and infectious etiologies in schizophrenia to include the investigation of T lymphocyte activation factors. We have begun to look at levels of interleukin 1 and 2, and soluable interleukin-2 receptor levels in the CSF and serum.

We concurrently evaluated CSF samples for antibodies, lymphocytes, or cytotoxic or cytotrophic factors, however, these nascent studies have not been fruitful and are being discontinued.

The third line of investigation involves studies in flow cytometry, T-lymphocyte mitogen function, and cytokine levels, to determine the effects of antipsychotic agents on immune function. Lymphocytes from the 4-East research ward patients are studied on a regular basis to test whether typical and atypical antipsychotic medication modifies immune function.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02345-02 NS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

EYE MOVEMENTS IN PSYCHIATRIC AND NEUROLOGIC PATIENTS AND NORMAL VOLUNTEERS

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Robert E. Litman, Senior Staff Fellow, Section on Clinical Studies, NS, NIMH

Others:	D. Pickar	Acting Chief	NS, NIMH
	D.W. Hommer	Medical Officer	VA
	T. Clem	Biomedical Engineer	BEIB, NIH
	E.I. Ginns	Chief, Unit on Mol Neurogenetics	NS, NIMH
	F. Torrey	Guest Researcher	NB, NIMH
	D. Daniel	Staff Fellow	CBDB, NIMH

COOPERATING UNITS *(if any)*

Department of Psychiatry, VA Medical Center, Seattle, WA; Biomedical Engineering and Instrumentation Branch, NIH; Neuropsychiatry Branch and Clinical Brain Disorders Branch, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.25	0.25

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Disorders of eye movement, particularly abnormal smooth pursuit eye movement (SPEM), remain one of the few specific neurologic findings in schizophrenia. Despite many studies which find eye movement disorders in schizophrenia, their precise nature and how they relate to the etiology and treatment of schizophrenia remain unclear. This project attempts to better define the pathophysiology of eye movement disorders by studying patients with schizophrenia, other neurologic disorders and normal controls utilizing a unique computerized infra-red oculo-graphic recording system which allows precise quantitative measurement of eye movement. We have observed and quantified differences in SPEM gain and saccadic intrusions in SPEM between schizophrenic patients and controls. We observed no effect of neuroleptic medication or clinical status on these differences in schizophrenic patients, confirming previous findings. However, we find that the atypical neuroleptic, clozapine, significantly reduces SPEM gain in schizophrenic patients treated with this medication. Also, in tests of saccadic eye movement, neuroleptic medication reduces the amplitude of predictive saccades. We observed in schizophrenic patients that the performance of SPEM and the ability to make anticipatory saccades in visually guided saccadic eye tracking tasks is correlated with performance on the Wisconsin Card Sort, a test of frontal lobe function. We also observed that caffeine, a dopamine agonist, improves SPEM performance by reducing saccadic intrusions in normal controls. Since a deficit in dopaminergic neurons arising from frontal cortex has been implicated as a possible mechanism for signs and symptoms in schizophrenia, our proposed course of study includes further comparison of eye movement with other tests of frontal lobe function and further study of the effects of dopamine agonists on eye movement in schizophrenic patients and controls. In addition, since it has been shown that deficits in eye movement may be inherited by unaffected first degree relatives of schizophrenic patients, eye movement and other tests of frontal lobe function in family pedigrees in collaboration with the Section on Molecular Neurogenetics.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02343-04 NS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Molecular Genetics of Inherited Neurologic and Psychiatric Disorders

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E.I. Ginns, Chief, Section on Molecular Neurogenetics, NS, NIMH

Others:	S.M. Paul	Acting Chief, Sect Molecular Pharmacology	NS, NIMH
	D. Pickar	Chief, Sect Clinical Studies	NS, NIMH
	J. Kelsoe	Medical Staff Fellow	NS, NIMH
	B. Martin	Visiting Scientist	NS, NIMH
	B. Stubblefield	Biologist	NS, NIMH
	S. Winfield	Microbiologist	NS, NIMH
	D. Klein	Chief, Sect Developmental Neurobiology	NICHHD

COOPERATING UNITS (if any)

Pediatrics Department, Johns Hopkins School of Medicine, Baltimore, MD; Florida Institute of Technology, Melbourne, FL; Dept of Anatomy & Neurobiology, Washington Univ School of Medicine

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Neurogenetics, Section on Preclinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	0.9	0.9

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We approached the characterization of the mutations responsible for inherited neurological or psychiatric disorders by studying the gene organization of specific proteins that might have a role in the pathogenesis of the clinical manifestations. Using the inherited lysosomal storage disorder, Gaucher disease, as a model, we demonstrated that the phenotypic heterogeneity seen within these inherited disorders is a consequence of different mutations, each affecting protein activity and influencing the processing, compartmentalization and/or stability of the protein. Southern analysis and polymerase chain amplification is used to identify mutations in Gaucher disease that frequently occur in both non-neuronopathic and neuronopathic phenotypes. The molecular mechanisms leading to nervous system involvement in these disorders have also been investigated. The results of this research should provide a more rational foundation for the diagnosis and formulation of therapeutic strategies for these inherited disorders. Similar approaches are being used to investigate the involvement of candidate genes in bipolar illness and other psychiatric disorders. Recombinant DNA techniques have been used to identify genes that may be involved in neuropsychiatric disorders. Genes specific for neurotransmitter biosynthesis (for example, human tyrosine hydroxylase and tryptophan hydroxylase) and receptors (for example, human GABA receptor) have been isolated. Linkage analysis and candidate gene identification continues in Amish bipolar patients. Recombinant DNA expression systems have been used to produce large amounts of brain proteins for structural and biochemical studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02342-04 NS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Gene Regulation within the Nervous System

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E.I. Ginns, Chief, Section on Molecular Neurogenetics, NS, NIMH

Others:	B. Martin	Visiting Scientist	NS, NIMH
	S. Winfield	Microbiologist	NS, NIMH
	J. Polak	Resident Scientist	RPMS
	J. Hozier	Medical Genetics	FIT

COOPERATING UNITS (if any)

Unit on Neurochemistry, Biological Psychiatry Branch, NIMH; Veterans Administration Medical Center, Durham, NC; Royal Post-Graduate Medical School, London, England; Florida Institute of Technology, Melbourne, FL

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Neurogenetics, Section on Preclinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.8	0.4	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We approached the cell-specific and developmentally regulated expression of proteins within the nervous system using the neuron specific (NSE) and non-neuronal (NNE) enolase isozymes as a model. Human brain cDNA and genomic DNA libraries were constructed so that the genes for these and other brain specific proteins could be isolated and characterized. Using both antibodies and oligonucleotide probes, cDNAs for both human NSE and NNE have been isolated and sequenced. Employing unique regions of these cDNA clones as probes, the developmentally and cell-specific regulated appearance of mRNA for each of these proteins can be investigated using in-situ hydridization. The human chromosome loci for each of these isozymes will be identified. In addition, the isolation of human genomic clones for each of these proteins should provide information on the regulation of expression of neuron and glial specific proteins during cell differentiation of the human nervous system in normal and disease states. The normal specificity of NSE for neural derived cell lines and the availability of specific DNA probes for NSE should provide a useful approach to the characterization of neural derived normal and tumor cell lineages.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02341-04 NS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Correction of Inherited Protein Deficiencies by Gene Transfer

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)
PI: E.I. Ginns, Chief, Section on Molecular Neurogenetics, NS, NIMH

Others:	B. Martin	Visiting Scientist	NS, NIMH
	E. Sidransky	Guest Researcher	NS, NIMH
	B. Stubblefield	Biologist	NS, NIMH
	M. LaMarca	Guest Researcher	NS, NIMH
	S. Winfield	Microbiologist	NS, NIMH
	B. Martin	Guest Researcher	NS, NIMH
	W. Eliason	Guest Researcher	NS, NIMH

COOPERATING UNITS (if any)
Center for Cancer Research, MIT and Whitehead Institute for Biomedical Research, Cambridge, MA

LAB/BRANCH
Clinical Neuroscience Branch

SECTION
Section on Molecular Neurogenetics, Section on Preclinical Studies

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	0.7	1.1

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The isolation and characterization of normal and abnormal proteins in genetic disorders affecting the nervous system has permitted the isolation of cDNA and genomic DNA that can be used to correct inherited protein deficiencies using recombinant DNA techniques, specifically somatic cell gene transfer. Particularly suited for initial attempts at gene therapy are those disorders (such as Gaucher disease, the most common sphingolipidosis) in which the manifestations of the disorder are due to abnormalities of hematopoietic cells, in this case, the macrophage. In this instance the transfer of normal genes to bone marrow progenitor cells is a rationale therapeutic approach. Using the lysosomal disorder Gaucher disease as a model, we have been successful in utilizing retroviral vectors to transfer and express human glucocerebrosidase in host mouse and Gaucher cell lines. The complete correction of glucocerebrosidase activity in Gaucher fibroblasts in culture has provided the impetus for evaluation of retroviral mediated somatic cell gene transfer of the glucocerebrosidase gene into mice by bone marrow transplantation. The initial goal of this research is the application of these recombinant DNA therapeutic strategies to the non-neuronopathic phenotypes. Animal models are being developed using recombinant technologies. Retroviral mediated transfer of tyrosine hydroxylase for the correction of DOPA deficiency is also studied. When our understanding of the pathogenetic mechanisms of inherited neurological and psychiatric diseases improves and when retroviral-mediated expression of genes in specific tissues and cells become more predictable, we can begin to investigate the potential usefulness of gene therapy for treatment of selected disorders affecting the nervous system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02340-04 NS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Biochemical and Clinical Studies of Gaucher Disease and Other Neurogenetic Disorders

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: E.I. Ginns, Chief, Section on Molecular Neurogenetics, NS, NIMH

Others:	W. Eliason	Guest Researcher	NS, NIMH
	M. LaMarca	Microbiologist	NS, NIMH
	B. Martin	Visiting Scientist	NS, NIMH
	B. Martin	Guest Researcher	NS, NIMH
	E. Sidransky	Guest Researcher	NS, NIMH
	B. Stubblefield	Biologist	NS, NIMH
	S. Winfield	Microbiologist	NS, NIMH

COOPERATING UNITS (if any)

Human Genetics Branch, National Institute of Child Health and Human Development; Interinstitute Genetics Program, NIH; Arthritis Service, Hospital for Joint Diseases, New York, NY

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Neurogenetics, Section on Preclinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.6	0.7	1.9

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The clinical study of human genetic disorders affecting the nervous system is important for the successful development of diagnosic techniques and strategies for therapy. This goal is also facilitated by a comprehensive knowledge of the biochemistry and clinical heterogeneity of the disorder. Gaucher disease, the most common sphingolipidosis, is extremely useful as a model because of the occurrence of both neuronopathic and non-neuronopathic phenotypes, as well as the broad spectrum of clinical diversity within the major types of the disorder, can be studied. Once the pathophysiologic mechanisms of systemic involvement in this enzyme deficiency disorder are understood, the therapy of nervous system dysfunction may be more rationally approached. Basic research on glucocerebrosidase, the enzyme deficient in Gaucher disease, has generated a more detailed understanding of the structure, biosynthesis, intracellular routing, and turnover of the enzyme. These studies will complement other studies within our branch focusing on the investigation of the potential and efficacy of gene transfer as a therapeutic approach. The use of recombinant DNA technologies both to develop appropriate animal models and to produce large amounts of both normal and mutant human proteins is being pursued.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02183-07 NS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Is Schizophrenia an Autoimmune Neuropeptide Receptor Disease?

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI: C.B. Pert, Guest Researcher, NS, NIMH

Others:	P. Laing	Visiting Associate & Guest Researcher	II, NS, NIMH
	B.M. Martin	Visiting Scientist	NS, NIMH
	M.H. Rapaport	Medical Staff Fellow	NS, NIMH

COOPERATING UNITS (if any)

Integra Institute

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Important progress has been made in the characterization of a novel 37 kDa protein (described in last year’s report) which may be an antigenic target for autoimmune reactions underlying virally-induced neuropsychiatric disorders. It’s presence in brain, adrenal medulla and pituitary suggest that it may be a presynaptic protein involved in neurosecretion. Although several attempts to clone this antigen (under the guidance of Dr. Ed Ginns) by immunological screening of cDNA libraries were unsuccessful, the finding that it is overexpressed in certain neuroblastoma cell-lines confirms it’s neuronal character and will facilitate future cloning attempts using appropriate neuroblastoma cDNA libraries depleted of non-neuronal messages by subtractive hybridization.

Using Dr. Fuller Torrey’s plasma samples from identical twins discordant for schizophrenia we found autoantibodies to specific brain proteins in the plasma of schizophrenics, including an antigen which was indistinguishable from the 37 kDa antigen by SDS electrophoresis. However, the occurrence of these antibodies was more frequent in unaffected twins, excluding the possibility that these antibodies are pathognomonic for schizophrenia.

We found antibodies to NGF-inducible high molecular weight neuron-specific proteins (MAP or neurofilament) of PC12 phaeochromocytoma cells in some Alzheimer patients. Antibodies raised to an NGF-like sequence in the influenza hemagglutinin identified a 50 kDa brain protein which may be a novel neurotrophic factor.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02181-07 NS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurobiology of Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: D. Pickar, Chief, Section on Clinical Studies NS, NIMH

Others:	S.M. Paul	Chief, Section on Molecular Pharmacology	NS, NIMH
	J.R. Kelsoe	Medical Staff Fellow	NS, NIMH
	P.E. Konicki	Medical Staff Fellow	NS, NIMH
	R.E. Litman	Medical Staff Fellow	NS, NIMH
	R.R. Owen	Medical Staff Fellow	NS, NIMH
	M.H. Rapaport	Medical Staff Fellow	NS, NIMH
	J.L. Schreiber	Social Worker	NS, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Cerebral Metabolism, NIMH; Clinical Brain Disorders Branch, St. Elizabeths Hospital, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7.0	5.0	2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project studies the psychobiology of schizophrenia and attempts to develop improved strategies for its treatment. One goal is the understanding of the mechanism of action of neuroleptic drugs. We have observed that neuroleptic-induced time-dependent decrease in levels of plasma homovanillic acid (HVA), a major peripheral dopamine metabolite, correlates with antipsychotic drug response, a finding consistent with the notion that slow to develop changes in dopamine turnover may underlie the antipsychotic action of neuroleptics. This clinically relevant dopamine marker is further studied using a strategy in which peripherally derived HVA is reduced by the administration of debrisoquin, a MAO inhibitor which does not enter the CNS. Longitudinal studies of the atypical neuroleptic, clozapine, have begun in in- and outpatient settings. This drug holds promise for enhancing the therapeutic effectiveness of neuroleptic treatment of schizophrenia and our studies are geared toward delineating fundamental mechanisms involved in its unique efficacy. In a recently completed study using magnetic resonance imaging (MRI) performed in collaboration with the Clinical Brain Disorders Branch, NIMH, compelling evidence was gained which supports enlargement of lateral and 3rd ventricular volumes in schizophrenic patients. A follow-up study of previous inpatients from our program has recently been completed and holds promise for delineating biological correlates of outcome in schizophrenia. Further studies of outcome are in progress. The development of extended pedigrees of families with high prevalence of schizophrenia is underway with the goal of establishing genetic linkage by RFLP techniques to the disease transmission. Collaboration with the NIMH positron emission tomography (PET) program focuses on the mechanism of action of typical and atypical neuroleptics using glucose utilization studies and on the development of new PET ligands.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02179-07 NS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Animal Models of Neuropsychiatric Disorders

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.N. Crawley, Chief, Unit of Behavioral Neuropharmacology		NS, NIMH
Others:	K. Laitinen	Guest Researcher	NS, NIMH
	M. Austin	Staff Fellow	NS, NIMH
	S. Cottingham	PRAT Staff Fellow	NS, NIMH
	E. Genc	Guest Researcher	NS, NIMH
	M. Schultzberg	Visiting Scientist	NS, NIMH
	S.M. Paul	Acting Chief, Sect Mol Pharmacol	NS, NIMH
	D. Pickar	Acting Chief	NS, NIMH

COOPERATING UNITS (if any)

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Pharmacology, NS, NIMH

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	3.0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Two new techniques, in situ hybridization and in vivo microdialysis, have been established in our laboratory to investigate catecholamines and coexisting neuropeptides, in brain regions involved in neuropsychiatric disorders.

In situ hybridization analysis of mRNA for tyrosine hydroxylase and cholecystokinin in midbrain dopaminergic neurons found no significant changes after acute or chronic haloperidol treatment. This finding suggests that the antipsychotic activity of haloperidol is not mediated at the level of transcription for neurotransmitter synthesis in the ventral tegmental or substantia nigra neurons.

Microdialysis studies of the mesolimbic dopaminergic pathway were designed to determine the peptidergic inputs to this pathway which have a major influence on dopamine release. Neuropeptides, including cholecystokinin, neurotensin, substance P, substance K, and oxytocin, were microinjected into the central region of the ventral tegmental area while microdialysis was performed in the posterior nucleus accumbens. Only neurotensin produced a robust increase in dialysate concentrations of dopamine, DOPAC, and HVA in the nucleus accumbens, suggesting that neurotensin inputs to the ventral tegmental neurons play a major role in regulating mesolimbic neuronal activity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02178-06 NS

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Pharmacology of Anxiety

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.N. Crawley, Chief, Unit of Behavioral Neuropharmacology,		NS, NIMH
Others:	M. Austin	Staff Fellow	NS, NIMH
	L. Morrow	PRAT staff fellow	NS, NIMH
	S. Paul	Acting Chief, Sec Molecul Pharmacol	NS, NIMH

COOPERATING UNITS (if any)

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	1.1	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The locus coeruleus has been implicated in stress responses and anxiety-related behaviors. In situ hybridization offers an approach to investigate whether locus coeruleus neurons respond to environmental challenges by increasing the synthetic activity at the level of transcription, to increase neurotransmitter availability. Hybridization with oligonucleotide probes for tyrosine hydroxylase, the rate limiting step in the synthesis of norepinephrine, and for galanin, a neuropeptide which coexists with norepinephrine in 80-90% of the locus coeruleus neurons, demonstrated a significant increase in mRNA for both tyrosine hydroxylase and galanin after reserpine treatment, but not after swim stress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02177-07 NS

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Behavioral Functions of Neuropeptides

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	J.N. Crawley	Chief, Unit of Behavioral Neuropharmacology	NS, NIMH
Others	S. DeMesquita	Visiting Scientist	NS, NIMH
	B. Martin	Visiting Scientist	NS, NIMH
	T. Podruchny	Psychologist	NS, NIMH

COOPERATING UNITS (if any)
Section on Molecular Neurogenetics

LAB/BRANCH
Clinical Neuroscience Branch

SECTION
Section on Molecular Pharmacology

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.70	1.70	1.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A. Galanin is a 29-amino acid peptide that coexists with acetylcholine in the septohippocampal pathway of the rat. We previously found that galanin inhibits the ability of acetylcholine to improve memory in a t-maze delayed alternation task, in rats with ventral forebrain lesions analogous to the degeneration seen in Alzheimer's disease. To determine the minimum critical amino acid sequence for the biological activity of galanin, the fragments 1-16, 17-23, 24-29, 12-29, 18-29, and 21-29 were tested alone and in combination with acetylcholine. C-terminal fragments as short as 6 amino acids acted as agonists, inhibiting acetylcholine on delayed alternation. The N-terminal fragment 1-16, which binds to the galanin receptor with an affinity equal to the parent peptide, increased choice accuracy when administered alone to lesioned rats. This finding suggests that galanin 1-16 is an antagonist of the galanin receptor, and that such an antagonist may improve memory in this animal model of Alzheimer's disease.

B. Microdialysis experiments were begun to test the hypothesis that neuropeptides are released in concert with the "classical" neurotransmitters with which they coexist, during behavioral events which activate the pathway of the coexistence. Rats were dialyzed for 1) dopamine and cholecystokinin in the medial posterior nucleus accumbens, before and after treatment with high potassium chloride in the dialysate, haloperidol i.p., or during Digiscan hyperlocomotion; and 2) acetylcholine and galanin in the ventral hippocampus, before and after treatment with high potassium chloride in the dialysate, scopolamine i.p., or during t-maze delayed alternation. Basal levels of neuropeptides were undetectable in all cases; some treatments produced detectable but variable increases in peptide concentrations from the dialysate. Analyses of percent recoveries revealed 0.2-4% for microdialysis, as compared to 60-100% for push-pull cannulae recoveries for both peptides.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-MH-02449-01 LDP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Long-term Effects of Father-Daughter Incest

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P. Cole	Senior Staff Fellow	LDP, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Childhood Behavior Disorders

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.20	.10	.10

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This series of retrospective studies on long-term effects of father-daughter incest focuses on the quality of relationships in the incestuous family of origin in relation to difficulties incest victims experience in their subsequent relationships in adulthood. Across studies, the victim's relationship with her mother is associated consistently with later interpersonal adjustment, more so than specific aspects of the nature of the sexual abuse, such as duration or the acts involved.

Victims who describe their mothers as uninvolved or negatively controlling or failing to believe the abuse was real report (1) significantly more marital distress, particularly in the areas of intimacy, trust, and affective communication, and (2) more difficulties in childrearing, particularly in the areas of consistency and autonomy promotion. Current work is aimed at (1) links between incest, adult personality disorder, and relationship problems with spouses and offspring, and (2) links between coping strategies during the abuse and adult psychopathology.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02448-01 LDP

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Prediction of Conduct Problems During the Transition from Preschool to School Age

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P.M. Cole	Senior Staff Fellow	LDP NIMH
CO-PI:	C. Zahn-Waxler	Chief, Section on Child Behavior Disorders	LDP NIMH
OTHERS:	G.L. Brown	Medical Officer	LDP NIMH
	N. Fox	Professor	U. Maryland
	M. Linnoila	Chief	LCS NIAA

COOPERATING UNITS *(if any)*
University of Maryland
Laboratory of Clinical Studies, National Institute on Alcohol Abuse and Alcoholism

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.72	1.50	.22

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of the study is to identify early predictors of stable conduct problems in young children. Although previous research indicates that antisocial personalities have histories of childhood behavior problems there is no scientific evidence by which to target young children at risk for developing antisocial patterns. This study assesses several known dispositional and familial correlates of antisocial personalities, with a particular focus on the development of self-regulation of angry and aggressive impulses. The findings will yield information for (1) profiling children at-risk for chronic problems, and (2) identifying factors which deter continuity of such problems. Patterns of continuity and discontinuity are to be examined in problem and nonproblem children beginning at age 4 through age 6. Observational data of children's emotional and behavioral control in a variety of interactions, psychophysiological recordings during different mood states, assays of biochemicals involved in behavioral regulation (such as serotonin), and cognitive assessment take place between ages 4-6. Psychiatric diagnoses and school adjustment are assessed between ages 6-7.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02447-01 LDP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Early Development of Prosocial and Aggressive Behavior

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. Zahn-Waxler	Chief, Section on Child Behavior Disorders	LDP, NIMH
Others:	M. Radke-Yarrow	Chief	LDP, NIMH
	J. Robinson	Project Coordinator, IBG	University of Colorado
	R. Emde	Professor	University of Colorado

COOPERATING UNITS *(if any)*

Institute for Behavior Genetics, University of Colorado,
Health Sciences Center, University of Colorado

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Child Behavior Disorders

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.40	.20	.20

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Sympathetic or empathic reactions may play an important role in inhibiting aggressive, antisocial, acts. This research focuses on the development of empathic behaviors in relation to aggressive acts in one- to three-year-old children. Children were observed in natural settings and in experimental situations. In one study, empathy and aggression were examined in 47 children. Concerned, prosocial behavior was found to develop in children between the ages of one and two, and to become increasingly more frequent and elaborated during this time period. Boys and girls did not differ in empathy, but boys showed somewhat more aggression. Empathy was related to reduced aggression, particularly for boys. The procedures developed to study empathy and aggression than were applied to a larger sample of 150 monozygotic and 150 dyzygotic pairs of twins. Behavior genetics analysis of heritability of empathy and aggression will begin in the fall of 1989. Preliminary analysis of empathic reactions indicates a similar pattern of development in twins as in singletons. In this larger sample, girls show more empathy than boys by the age of 14 months. The goal of this basic research is (a) to describe the early development of caring and harmful behaviors toward others and (b) to identify both genetic and environmental factors that contribute to individual differences in these characteristics.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02446-01 LDP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Postpartum Depression and the Development of Mother-Child Relations

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E. D. Nottelmann	Statistician	LDP NIMH
OTHERS:	G. P. Chrousos	Senior Investigator	DEB NICHD
	D. Rabin	Guest Researcher	DEB NICHD
	P. Gold	Chief	CNE NIMH
	M. Kling	Medical Officer	CNE NIMH
	D. Rubinow	Clinical Director	NIMH

COOPERATING UNITS *(if any)*

Developmental Endocrinology Branch, NICHD
Clinical Neuroendocrinology Branch, NIMH

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.10	.05	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The development of mother-child relations is investigated in a sample of 100 primiparous women enrolled in a prospective interdisciplinary study of endocrine, psychiatric, and psychological factors in post-partum depression (Clinical Project No. 88-CH-120). This study, which will draw on the data from the larger study, is specifically concerned with the development of mother-child relations. During the first three months postpartum, the growth and development of infants will be assessed and interactions between the mother and infant will be evaluated. Results will be compared for women who develop postpartum depression with those for pregnant women who do not develop postpartum depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02445-01 LDP

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Course of Offspring Problems in Relation to the Course of Parental Illness

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.D. Nottelmann	Statistician	LDP NIMH

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.42	.10	.32

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The study follows the course of children's patterns of problems (timing, severity, and type of problem) over time in conjunction with the course of parents' depression (timing of episodes, severity, treatment, family context), in order to investigate the interdependencies among level of children's development, children's problems, family environment, and parents' depressive symptomatology.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02443-01 LDP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Potential Impact of Psychiatric Treatment upon Mother-Child Communication

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K. Free	Staff Fellow	LDP, NIMH
Others:	W. Habelow	Research Psychologist	LDP, NIMH
	C. Zahn-Waxler	Chief, Section on Child Behavior Disorders	LDP, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.27	.15	.12

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Affective language between depressed mothers and their children is examined to determine whether differences in mothers' psychiatric treatment corresponds to differences in their ability to talk with their children about feelings. This involves assessing (1) mother's accuracy in interpreting emotional expression to her child, (2) mother's ability to correct her child's inaccurate interpretation of facial expressions, (3) mother's ability to facilitate her child's communication about emotions, and (4) mother's ability to qualify and elaborate discussion in emotion terms. Mothers who have had a verbally based therapy are expected to be more able to explore feelings and emotions with their children than are mothers who have had no treatment or had pharmacotherapy alone.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02442-01 LDP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Suicidal Thinking in the Children of Depressed and Well Parents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K. Free	Staff Fellow	LDP, NIMH
Others:	G. Brown	Medical Officer	LDP, NIMH
	M. B. Fox	Staff Psychiatrist	LDP, NIMH
	M. Radke-Yarrow	Chief	LDP, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Affective Disorders

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.47	.25	.22

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The aims of this study are to determine the occurrence and nature of suicidal thoughts in children of depressed and well parents, and to investigate whether children of suicidally depressed parents are at a greater risk for developing suicidal symptoms than are children of parents who are not suicidally depressed. The subjects are participants in the longitudinal Child Rearing Project (MH-02144). This longitudinal sample includes 123 families of bipolar, unipolar depressed, and well parents, i.e., mother, father, and two sibling children. From multiple data sources -- a psychiatric interview with child, interviews with the parents about the child, reports on the Child Behavior Check List -- data were obtained about the child's thoughts and/or plans about hurting him/herself or wishing to die. Analyses based on two assessment periods are now in progress regarding a) frequency and age of symptom appearance, b) relation between manifestations in parent and child symptoms, c) relation of suicidal ideation to parent and child diagnostic status and personality variables, and d) relation of suicidal thinking to life events and circumstances.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 MH 02417-02 LDP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Aggression and Social Competence in Young Children: A Longitudinal Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. Zahn-Waxler	Chief, Section on Child Behavior Disorders	LDP, NIMH
Others:	E. Cummings	Associate Professor	University of West Virginia
	K. Rubin	Professor	University of Waterloo
	S. Denham	Associate Professor	George Mason University
	R. Iannotti	Research Psychologist	Georgetown University

COOPERATING UNITS *(if any)*
University of West Virginia, University of Waterloo,
George Mason University, Georgetown University

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION
Child Behavior Disorders

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this research is to identify, early in development, characteristics of children that predict problem behaviors at school age. Young children's interactions with other children were examined because problems in peer relations are good predictors of later social-emotional problems and psychiatric disorders. Forty-eight children of depressed and well mothers were observed and assessed using naturalistic and experimental procedures, at age 2 and again at age 5. At age 6 psychiatric assessments were made. Significant age changes, as well as continuity over time, were identified in children's aggression, affect and social skills. The social skills of children of well mothers increased with age. The peer relations of children of depressed mothers were compromised: they showed negative emotion, lack of frustration tolerance, social deficits and little involvement in the environment. Early deficits in modulating emotions in social relationships may precede more formal manifestations of psychiatric problems in children, and thus may serve as early marker variables.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02415-02 LDP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Longitudinal Psychiatric Status: Parent, Offspring

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	G. Brown	Medical Officer	LDP NIMH
OTHERS:	K. Free	Staff Fellow	LDP NIMH
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:

PROFESSIONAL:

OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

  ☒ (a1) Minors

  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The work described in this analysis has been incorporated in the expanded study of children's psychosocial developmental course described in the Psychiatric Status of Children of Depressed Parents, Z01 MH-02372-03.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02411-02 LDP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Sleep Disturbances in Young Children of Mothers With An Affective Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.D. Nottelmann	Statistician	LDP NIMH
OTHERS:	S. Stoleru	Chef de Clinique-Asst	General Henrion Bertier, France

COOPERATING UNITS *(if any)*

General Henrion
Bertier, Nevilly-Sur-Seine, France

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.27	.05	.22

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The incidence and stability over time of sleep disturbance, based on mothers' reports, are examined in children whose mothers have a diagnosis of bipolar depression, children whose mothers have a diagnosis of unipolar depression, and well mothers. Mothers' reports were obtained twice on two of their children: (a) on the younger children when they were between 2 and 3 1/2 years old and again when they were between 5 and 6 1/2 years old; and (b) on the older children when they were between 5 and 8 years old and again when they were between 8 and 11 years old. In addition, sleep problems in these children are examined in relation to incidence of depression in parents; i.e., in children who have two depressed parents, children who have one depressed parent, and children who have no depressed parents.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH-02410-02 LDP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Observational Assessment of Parent and Child from Toddlerhood to Late Childhood

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E. Nottelmann	Statistician	LDP NIMH
CO-PI:	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.97	.35	.62

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The longitudinal study of children of depressed and normal parents has as an important objective, the tracking of the individual child's behavioral development from toddlerhood to late childhood and early adolescence. A major data source is systematic observation of behavior in contexts which, theoretically, sample significant aspects of (a) developmental progress and (b) parent-child interaction. Behavioral assessments are made in terms of the child's regulation of his/her own behavior, affect (expression, use, and regulation), verbal communication, self-conception, and relationships. Behavioral coding is also conceptualized to be compatible with child assessments from other sources (e.g., psychiatric interview, parent reports, psychological tests). The family context, particularly the mother's behavior with the child is an integral part of the observations over time.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH-02409-02 LDP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Differential Development of Siblings in Shared and Nonshared Family Environments

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI;	E. Nottelmann	Statistician	LDP NIMH
CO-PI:	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.22	.10	1.12

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Children in the same family often differ significantly in psychological characteristics and behavioral outcomes. They show significant resemblances. Although these facts are well known, the processes by which family environments are linked to sibling differences and similarities are only partly understood. Such understanding is critical to developmental theory and to theories of gene-environment interactions. The purpose of this study is to investigate the shared and nonshared family experiences of siblings in relation to their similar and different social and emotional development. The research has three objectives. The first is descriptive -- what are the family experiences of siblings? The second concerns the links between siblings' shared and nonshared family experience and the developmental course of each sibling. The third is to investigate child-specific attributes (temperament, gender, age, and others) that interact with environment and with environmental influences on sibling development.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02408-02 LDP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders.)*

Competency in Children at Risk for Psychiatric Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K. Free	Staff Fellow	LDP, NIMH
Others:	W. Habelow	Research Psychologist	LDP, NIMH
	E. Nottelmann	Statistician	LDP, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Affective Disorders

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.47	.15	.32

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of the study is to explore the competencies of a sample of children at risk for psychiatric disorder and to examine the development of these competencies from a longitudinal perspective. Physical, cognitive, and social competencies are examined cross-sectionally and longitudinally. The children are two siblings in 123 families participating in the longitudinal Child Rearing Project (MH-02144), including families with bipolar and unipolar depressed parents and well parents. Data on the children's competencies are based on mother report (Child Behavior Check List). The psychiatric status of parents is based on standard psychiatric interviews (SADS, RDC criteria).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 MH 02381-03 LDP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Functioning of Depressed Mothers In and Between Episodes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. Richters	Senior Staff Fellow	LDP, NIMH
Others:	M. Radke-Yarrow	Chief	LDP, NIMH
	D. Pellegrini	Psychologist	Catholic University

COOPERATING UNITS *(if any)*
Catholic University

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION
Affective Disorders

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.77	.25	.52

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Are maternal childrearing behavioral deficits characteristic of women with a history of depression, or are difficulties present only when mothers are experiencing an acute episode of depression? Are there certain patterns of aberrant child-related behaviors that wax and wane with depressive episodes, and others that reflect more or less enduring behavioral characteristics of depressed mothers? In this longitudinal study it is possible to compare maternal characteristics of two groups of mothers with a history of affective disorder: those who are in an episode and those who are between episodes of depression at the time of their participation in the study, when they are observed with their children. Depressed mothers who are functioning as the principal childrearing agent and who are currently in episode were found not to be more likely than those who are not in episode to report behavior problems in their children. Both groups, however, report significantly more child behavior problems than mothers without a history of depression. In forthcoming analyses the behaviors of mothers with their children are the dependent variables: Do depressed mothers in episode and those not in episode differ in communication patterns, affect, and control practices with their children? Are the children and the mother-child relationship more problematic with mothers who are in episode than with mothers who are not in episode?

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02380-03 LDP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Stressful Life Events and Childhood Adjustment

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. Richters	Senior Staff Fellow	LDP, MINH
Others:	D. Pellegrini	Psychologist	Catholic University
	M. Radke-Yarrow	Chief	LDP, NIMH

COOPERATING UNITS *(if any)*

Catholic University

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Affective Disorders

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.44	.72	.62

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The objective is to investigate the links between parental psychopathology, stressful life events, and the social-emotional adjustment of children. The analyses are based on data from families participating in the longitudinal study (Z01 MH 02144), which includes children of parents with and without a history of affective disorder (based on psychiatric SADS-L interviews). Data on stressful life events to which the children have been exposed are obtained in intensive, semi-structured interviews with mothers. Assessments of children's functioning are based on reports from parents and teachers. Families with a depressed parent (or parents) have significantly higher than average levels of marital distress, health problems, financial problems, housing problems, job difficulties, relationship problems and spouse maladjustment. Moreover, the depressed women evidenced significant levels of maladjustment and/or incompetence in coping with these problems. Differences between families with and without a depressed parent are sufficiently strong that knowledge of these aspects of family life allows us to correctly predict (via discriminant function analysis) the depressed or normal status of 84% of the families.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02372-03 LDP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychiatric Status of Children of Depressed Parents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Radke-Yarrow	Chief	LDP NIMH
OTHERS:	G. Brown	Medical Officer (Psychiatry)	LDP NIMH
	L. Cytryn	Guest Scientist (Psychiatry)	LDP NIMH
	M. Fox	Medical Staff Fellow	LDP NIMH
	D. McKnew	Guest Scientist (Psychiatry)	LDP NIMH
	E. Nottelmann	Statistician	LDP NIMH
	J. Richters	Senior Staff Fellow	LDP NIMH
	K. Free	Staff Fellow	LDP NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.75	2.45	.30

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This is a longitudinal study of children born to, and reared by, depressed parents, and a comparison group of children of parents without histories of, or current psychiatric problems. Children are studied from early childhood to early adolescence. The present analyses focus on the psychiatric assessments of the children at successive age levels. Children of parents with major depression, bipolar depression, or without psychiatric illness are compared. Based on the psychiatric play interview, a substantial number of children (40%) are evaluated by the clinician as manifesting behaviors of some clinical concern of (e.g., separation anxiety, disruptive behavior, developmental delay). Children of the bipolar mothers are seen as least problematic. These assessments alert one to the difficulties in separating normative behaviors at this early age from deviant problem behaviors. At the older ages (5 to 6 and 8 to 11 years), less than 10% of the children in the control group manifest clusters of problems evaluated as severe by the clinician. In the groups of unipolar and bipolar offspring, severe problems appear in 22% of the children at 5 to 6 years, and 36% of the children at 8 to 11 years. There is not a single predominant type of problem.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02370-03 LDP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Caregiving Patterns in Stressed Families

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	F. Bridges-Cline	Guest Researcher	LDP NIMH
OTHERS:	W. E. Wilson	Guest Researcher	LDP NIMH
	M. Radke-Yarrow	Chief	LDP NIMH
	D. Hay	Research Psychologist	U. of London
	T. Cox	Psychiatrist	U. of Liverpool

COOPERATING UNITS *(if any)*

University of London
University of Liverpool

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.37	.10	.27

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Of primary interest in this research is the functioning of different sorts of families with respect to a central dimension of family life, the provision of care to its members. An additional aim of the study is the examination of associations of parental depression and other family stressors with varying patterns of family caregiving.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH-02369-03

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mutual Mother-Child Influences in Families With and Without Affective Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	G. Kochanska	Senior Staff Fellow	LDP NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: .62	PROFESSIONAL: .40	OTHER: .12

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Processes of mutual interpersonal influence are studied in dyads comprised of well and depressed mothers and their 5-year-old children. This is a longitudinal study, following up the sample of 87 dyads in which control and discipline interactions were studied when the children were 1 1/2 to 3 1/2 years old (Z01 MH-02144). The study is focused on difficulties of depressed mothers in controlling their children, and on the development of children's competent interpersonal responses to control. Both issues were investigated in the initial study. Two major research questions are addressed: What is the relation between the mother's psychopathology and the processes of interpersonal influence between mother and child, and what are the developmental changes from the time the child was two to when s/he was five years of age? In contrast to the first study, where the focus was on the mother as the agent of control and child as a respondent, in this study the focus is on bilateral interpersonal influence processes. These bilateral influence processes are studied by analyzing every episode of control, initiated either by the mother or by the child, during naturalistic interaction. Toddler-age findings, that daughters of depressed mothers were more noncompliant, were also replicated at five years. In contrast to the toddler-age findings, when the well mothers provided more structure than the depressed mothers, at five the opposite was true -- the well mothers were less direct and assertive than the depressed mothers, relying more on the children's increased capacity for self-regulation. From the longitudinal comparisons, it appears that the depressed mothers failed to make appropriate developmental adaptations to their children's increasing capacities of self-regulation. However, in both groups robust developmental changes in maternal strategies, as well as in children's responses, were identified. More evidence was also found regarding adaptive and maladaptive response style, as well as maternal strategies of influence.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02368-03 LDP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Dissociative Experience Scale (DES)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	F. Putnam	Staff Psychiatrist	LDP, NIMH
Others:	M. Demitrack	Staff Psychiatrist	CNB, NIMH
	E. B. Carlson	Assistant Professor	Marquette University

COOPERATING UNITS *(if any)*

ENB, NIMH;
Marquette University

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Childhood Behavior Disorders

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.37	.25	.12

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Dissociative Experiences Scale (DES) is a short, self-administered questionnaire that reliably and validly discriminates patients with major dissociative psychopathology from other psychiatric patients and normal controls. The DES has been well-received in the research community and is now included in over 60 on-going research studies. Our initial study on the reliability and validity of the instrument has been replicated by several groups. Current NIMH, IRP research using this instrument includes studies of the following patient groups: dissociative disorders, borderline personality disorder, anxiety/phobic disorders, affective disorders and eating disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02367-03 LDP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Clinical Phenomenology of Multiple Personality Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	F. Putnam	Staff Psychiatrist	LDP, NIMH
Others:	R. Post	Chief	BPB, NIMH
	R. Loewenstein	Senior Psychiatrist	Sheppard Pratt Hospital

COOPERATING UNITS *(if any)*

Sheppard Pratt Hospital, Baltimore, Maryland

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Childhood Behavior Disorders

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.37	.25	.12

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☒ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The clinical syndrome of Multiple Personality Disorder (MPD) is a major dissociative disorder that is increasingly recognized in victims of severe childhood abuse. Although this condition has been identified for over two hundred years, little is known about its long term outcome. At present there are over 7000 identified cases in the United States with additional cases being added at an extremely rapid rate reflecting a growing awareness of the condition. We have systematically collected data on over 200 cases in treatment in the United States. Our findings indicate that MPD is a clinical syndrome with a core of dissociative and affective features that occurs in individuals suffering serious, repetitive childhood trauma (primarily physical and sexual abuse) between ages two to 14 years of age. The disorder is typically not diagnosed until the third to fourth decade with victims receiving an average of 3.4 misdiagnoses and 6.8 years of treatment for conditions that they do not have. Proper treatment appears to substantially reduce the morbidity but no systematic controlled treatment outcome studies have been conducted to date.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02366-03 LDP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Psychophysiology of Multiple Personality Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	F. Putnam	Staff Psychiatrist	LDP, NIMH
Others:	R. Post	Chief	BPB, NIMH
	T. Zahn	Research Psychologist	LPP, NIMH
	J. Grafman	Chief, Cognitive Neuroscience Unit	MNB, NINCDS
	H. Weingartener	Chief	CCS, NIMH
	P. Turkeltaub	Staff Psychiatrist	FDA

COOPERATING UNITS *(if any)*

BPB, NIMH; LPP, NIMH; MNB, NINCDS; CCS, NIMH; Food and Drug Administration

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Childhood Behavior Disorders

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.37	.25	.12

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project seeks to characterize and quantify psychophysiological differences that occur across the alter personality states of individuals with multiple personality disorder (MPD). Alter personalities of MPD patients are studied using a range of psychological, physiological and biological measures including: spontaneous EEG, auditory and visual evoked potentials, cerebral blood flow, histamine sensitivity, psychological tests and indices of autonomic nervous system activity. Simulating normal controls subject serve as a comparison group.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 MH 02365-03 LDP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Psychobiological Effects of Sexual Abuse

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	F. Putnam	Staff Psychiatrist	LDP, NIMH
Others:	P. Trickett	Guest Researcher	LDP, NIMH

COOPERATING UNITS *(if any)*
Chesapeake Institute, Wheaton, Maryland; Montgomery County, MD, Child Protection Unit; Division of Child Protection, Children's Hospital National Medical Center, DC; Prince George County, Division of Child Protection; Fairfax County, VA, Child Protection Services.

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION
Childhood Behavior Disorders

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.60	.80	.80

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project comprises a series of studies focusing on the psychological and biological effects of sexual abuse in female children. Subjects are sexually abused females (aged 6-15 years) and a non-abusing parent or legal guardian. Control subjects are matched for age, SES and one- or two-parent living situations. The project uses a multi-method approach to gather data on the psychological and physical development of these children. Methods include: Tanner staging of physical development, blood hormone levels, psychological tests of the children and developmental interviews from the parent or guardian. Three broad categories of hypotheses are tested: 1) that sexually abused girls will have significantly more difficulty during the transition through puberty, particularly with respect to sexual and aggressive behaviors; 2) that sexual abuse may effect specific hormonal levels and alter the timing and onset of puberty; 3) that sexually abused girls will demonstrate higher levels of dissociative behavior and maintain these dissociative behaviors into adolescence compared to control subjects who are predicted to show a decline in normative childhood dissociative behaviors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH-02361-03-LDP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Multi-Method Assessment of Children's Psychosocial Development

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Radke-Yarrow	Chief	LDP NIMH
OTHERS:	E. Nottelmann	Statistician	LDP NIMH
	J. Richters	Senior Staff Fellow	LDP NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: .77	PROFESSIONAL: .40	OTHER: .37

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In the longitudinal investigation of children's psychosocial development in relation to parental psychopathology, we have utilized a multi-method approach in estimating child "outcomes" at successive ages. Within a psychiatric framework, such as DSM-III, the child's psychosocial status is assessed in terms of one or more diagnostic labels. Assessments in developmental terms are made along specific behavioral or attitudinal dimensions. This maximizes the breadth and sensitivity of assessment of children: How similar are child evaluations from different measures and from different sources? For what kinds of information are different methods best adapted? How suited are different methods to children of different ages and backgrounds?

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02233-04 LDP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Development of Guilt: Language, Emotions, and Behavior

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. Zahn-Waxler	Chief, Sec. on Child Behavior Disorders	LDP NIMH
OTHERS:	G. Kochanska	Senior Staff Fellow	LDP NIMH
	P. Cole	Senior Staff Fellow	LDP NIMH
	K. Barrett	Assistant Professor	Univ. of Wyoming

COOPERATING UNITS *(if any)*

University of Wyoming

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Child Behavior Disorders

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.90	.20	.70

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

While feelings of sadness predominate in depression, the disorder is characterized by dysregulation of a number of other emotions as well (e.g., anxiety, irritability and guilt). Pervasive guilt or feelings of responsibility for negative events are synonymous with some definitions of depression. Understanding of the etiology of depression would be advanced by research on the origins and development of core emotions associated with the disorder. Fifty-five children were seen in experimental paradigms designed to assess dispositions to experience guilt. By age two, most children showed some guilt, but there were consistent individual differences and gender differences as well. Girls more than boys showed guilt over harming others, and girls' behavioral expressions of guilt (i.e., reparative acts) were more clearly linked to emotions of sadness and anxiety. An early tendency to experience guilt may combine with environmental factors to predict later affective problems in which guilt is prominently featured.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02231-05 LDP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biological-Behavioral Relations in Early Adolescence

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.D. Nottelmann	Statistician	LDP NIMH
OTHERS:	E.J. Susman	Guest Researcher	LDP NIMH
	G.I. Germain	Research Psychologist	LDP NIMH
	L.D. Dorn	Guest Researcher	LDP NIMH
	G.P. Chrousos	Senior Investigator	DEB NICHD
	G.B. Cutler, Jr.	Senior Investigator	DEB NICHD

COOPERATING UNITS *(if any)*

Developmental Endocrinology Branch, NICHD

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.60	.20	.40

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Interrelations of markers of pubertal development and adolescent adjustment and behavior are investigated cross-sectionally and longitudinally. Participants are 9- to 14-year-old boys and girls and their parents. The adolescents and their parents are seen three times, six months apart. The markers of pubertal development include serum hormone levels (gonadotropins, sex steroids, and adrenal androgens), pubertal stage (Tanner criteria), and height and weight. Psychological assessments of the adolescent include adolescent- and parent-report of behavior problems and competencies. Behavioral observations of parents and their adolescent in family interactions also were made. To assess the robustness and generality of findings, hormone-behavior relations were examined at three times of measurement. A conservative replication test was carried out, using hormone factor scores (aggregating across individual hormones) and behavior composite scores (aggregating across source of data, methods, and instruments). Sets of multiple regression analyses were conducted, with various controls. Although findings did not extend to all domains of adolescent psychosocial functioning, hormone-behavior relations were detected and replicated in most cases (i.e., were similar at two or three times of measurement). For boys, higher adrenal axis hormones were associated with a higher degree of irritability, attitudinal problems, and peer and family relationship problems. Also, for boys, higher gonadal axis hormones were associated with a higher degree of problems in academic performance. For girls, higher gonadal axis hormones were associated with higher degrees of problems involving affective problems and peer as well as family relationship problems. In general, findings replicated previous reports based on data from the first time of assessment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH-02229-05 LDP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Vocalic Analysis of Natural Discourse in Well and Depressed Mothers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. Sherman	Research Psychologist	LDP NIMH
OTHERS:	Z. Breznitz	Assistant Professor	U. of Haifa

COOPERATING UNITS *(if any)*

University of Haifa, Israel

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.22	.10	.12

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Investigation of verbal communication between mothers and their 2- to 3-year-old children indicated differences between well and depressed mother-child dyads. Vocalization was significantly lower in the depressed dyads except in situations involving mild stress. The long-term characteristics of these impairments were examined when the families were reassessed three years later. Conversation between mother and child and child and sibling was analyzed.

Findings of lower rates in depressed mother-child discourse are replicated. Rates of discourse between siblings, however, show no group differences. Thus, the siblings appear to provide an alternative environmental support to each other when this support is not readily available from the mother.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH-02207-06 LDP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Affective Rearing Environment: A Comparison of Normal and Depressed Parents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Radke-Yarrow	Chief	LDP NIMH
OTHERS:	E. Nottelmann	Statistician	LDP NIMH
	G. Kochanska	Senior Staff Fellow	LDP NIMH
	L. Kuczynski	Associate Professor	U. of Guelph

COOPERATING UNITS *(if any)*

University of Guelph, Guelph, Ontario, Canada

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.12	.35	.77

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

- ☒ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Moods and emotions carry much of the meaning of mother and child interactions and relationships. How mother and child express and use affect, and how they respond to affect of the other person are investigated. The source of data is the longitudinal study of unipolar and bipolar depressed parents and well parents (MH-02144) and their toddler children. In the naturalistic laboratory paradigm, the families are observed for two 3-hour periods. Continuous recording is obtained of mother's and child's affective expression. Time is divided into one-minute units; each unit is coded for predominant affect. The children are between 1 1/2 and 3 1/2 years of age. Children of the depressed mothers tend not to be on a good developmental course with regard to emotion regulation and positive relationship with mother. Boys and girls are developing in different affective contexts, especially when mothers' psychiatric status is taken into account. Girls of depressed mothers have the least favorable affective context.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02171-06 LDP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Protective and Risk Factors in Childrearing: Contributions of Fathers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. Richters	Senior Staff Fellow	LDP, NIMH
OTHERS:	M. Radke-Yarrow	Chief	LDP, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Affective Disorders

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.27	.15	.12

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The husbands of depressed women may buffer their children from the stresses resulting from depression-related childrearing impairments in the mother. The husbands may also increase the stresses to which the children are exposed by not functioning effectively or by manifesting impairments of their own. The objective of this study is to examine the functioning of the fathers and their impact on the child.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02170-07 LDP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychiatric Assessment of Infants and Toddlers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Cytryn	Guest Scientist (Psychiatrist)	LDP NIMH
OTHERS:	T. Sherman	Research Psychologist	LDP NIMH
	D. McKnew, Jr.	Guest Scientist (Psychiatrist)	LDP NIMH
	A. Mayfield	Social Science Analyst	LDP NIMH

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Section on Affective Behavior

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.27	.90	.37

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The aim of this project is to develop a framework and a method for the psychiatric evaluation of children ages 2 to 4 years of age. The objective is to develop meaningful classifications of toddler-age children that will reliably differentiate children of these ages and will be predictive of psychiatric status at a succeeding stage of development. A second goal is to develop a procedure that is useful not only in research but also in clinical practice. One hundred children between 2 and 3 1/2 years of age, offspring of unipolar and bipolar depressed parents and well parents, constitute the sample (Z01-MH-02144). Families are of middle- to upper-middle-class background. The method, described in detail in previous reports, makes use of psychiatric assessments of 2- to 3 1/2-year-old-children in two kinds of circumstances: a semi-controlled play interview with a psychiatrist and a series of standard situations of child-mother interaction. Evaluations are made in terms of the child's relationships, mastery, mood, and control of mood. Clusters of behaviors in these terms are translated into assessments of "risk", from 0 (no clinical concern) to 4 (sufficient concern to recommend that parent seek immediate help for the child). The child is evaluated on degree and kinds of risk. The children are evaluated again three years later. The assessment is based on a standard interview with the child, with mother's reports an additional source of information. The psychiatrist making this evaluation is totally unfamiliar with the children and their families.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02156-10 LDP

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Personality of Children Reared by Normal and Depressed Mothers: Inhibited Children

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	F. Bridges-Cline	Guest Researcher	LDP NIMH
OTHER:	G. Kochanska	Senior Staff Fellow	LDP NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.25	.10	.15

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study examines maternal depression as a contributory factor to early childhood inhibition. Patterns of child behavior in the face of the unfamiliar (persons, places) such as behaviors expressing inhibited exploratory activity and social withdrawal are observed at 2 to 3 years of age in semi-naturalistic but standard settings, which represent varied contexts of unfamiliarity. Analyses of these data revealed that six reliable dimensions of mother and child response styles could be empirically derived from our observation coding system. Comparison of these response styles across maternal diagnostic groups indicated that the impact of maternal depression is clearly dependent on the sex of the child and the type of pathology of the mother. Specifically, the girls of the major depressed mothers appear to be uniquely sensitive to their mother's depression, as manifest by the strongly inhibited response styles of these children, and this sensitivity appears to be a linear function of the severity or intensity of the mother's depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH-02152-10 LDP

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Discipline and Parental Control in Families with Affective Disorders

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	G. Kochanska	Senior Staff Fellow	LDP NIMH

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.45	.30	.15

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Mothers' discipline and control practices directed to their young children were studied in well and clinically depressed mothers. Depressive symptomatology has been linked to inappropriate control practices, but specific difficulties of depressed mothers and possible implications for their children's development have not been identified. Parental childrearing skills are particularly critical during the period between 1 1/2 and 3 1/2 years of age. The development of autonomy, expressed by the increase in noncompliance to parental pressure, and the development of self regulation, expressed by the increase in compliance with caregivers are two conflicting themes in child development during that period.

Assessments of mother and child behaviors are based on observations of their interactions in a naturalistic setting (see Annual Report MH 02144). This year analyses are a continuation of the previous year's work. The focus is on the specific control strategies used by well and depressed mothers. Analyses revealed that depressed mothers, compared to well mothers, have specific difficulties controlling their children. They show a pattern of verbal control strategies, indicative of less assertiveness and less directness, and more fear of confrontation toward their children than the pattern manifested by well mothers.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02038-07 LN

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Ontogenetic development and decline of cognitive memory and habit formation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.H. Bachevalier	Guest Researcher	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	L.G. Ungerleider	Research Psychologist	LN NIMH
	D.P. Friedman	Deputy Director	DPR NIDA
	C.S. Hagger	Guest Researcher	LN NIMH
	P.M. Merjanian	Postdoctoral Fellow	LN NIMH
	M.J. Webster	Postdoctoral Fellow	LN NIMH

COOPERATING UNITS *(if any)*

Division of Preclinical Research, NIDA University of North Carolina
The Johns Hopkins University
Laboratory of Comparative Ethology, NICHHD

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	0	3.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cognitive memory and habit formation are two qualitatively different learning processes based on separate neural systems, a cortico-limbic and a cortico-nonlimbic system, respectively. To see how emotional and social behavior develop in animals whose infantile global amnesia might persist from infancy through adulthood, we have prepared monkeys with neonatal limbic lesions and followed their behavioral development. Animals with neonatal removal of cortical area TE, a higher-order visual station linked to both learning systems, serve as controls. Assessment of the effects of these neonatal lesions on the early development of habits and memories points to greater compensatory potential after neonatal cortical than after neonatal limbic removals. In addition, the long-term effects of these early lesions indicate that compensatory mechanisms operate early to promote permanent recovery from neonatal temporal cortical but not from neonatal limbic lesions. These findings suggest that association areas of the cortex are immature at birth, and may thus possess greater plasticity than limbic structures. Direct evidence of neocortical immaturity in the macaque has been provided by our neurobiological studies on opiatergic and cholinergic receptor distribution and on metabolic activity. Data on both normal and operated infants suggest that development of the nonlimbic habit system is sexually dimorphic, and that this is due to the high testosterone levels present in male infants before and shortly after birth. Interestingly, early damage to the limbic memory system produces later socio-emotional abnormalities. The developmental time course and the nature of these disturbances resemble those seen in autistic children. Finally, the studies in young adult monkeys together with those in normal aged animals are providing the anatomical and chemical basis for understanding the memory disorders in humans that accompany cerebrovascular and other cerebral accidents and diseases as well as the gradual decline in memory ability that occurs with normal aging.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02037-08 LN

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Functional anatomy of the somatosensory cortex of macaques

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T.P. Pons	Staff Fellow	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	P.E. Garraghty	Research Associate	Vanderbilt U.
	D.P. Friedman	Deputy Director	DPR NIDA
	S.L. Juliano	Assistant Professor	USUHS
	E.A. Murray	Senior Staff Fellow	LN NIMH
	M.E. Huerta	Assistant Professor	U. of Conn.
	R.C. Saunders	Research Psychologist	CDB NIMH

COOPERATING UNITS *(if any)*

Division of Preclinical Research, NIDA   University of Connecticut
Vanderbilt University
Uniformed Services University of the Health Sciences

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects   ☐ (b) Human tissues   ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

By use of anatomical markers to trace the connections between somatosensory cortical fields, we have identified two possible routes by which somatosensory information could reach limbic structures important for somatosensory memory. One route courses dorsally from the postcentral strip through posterior parietal cortex and has access to the limbic system via cingulate cortex. This pathway may be functionally analogous to the occipitoparietal pathway for spatial vision. The second route courses ventrally from the postcentral strip through SII and insular cortex to the amygdala and indirectly to the hippocampus through rhinal cortex. We now have strong evidence that this second pathway is analogous to the occipitotemporal pathway for object vision. First, by recording single- and multi-unit activity from the SII region in hemispheres that had received lesions of selected portions of the postcentral body representation, we have demonstrated loss of the corresponding representation from SII, indicating that at least this part of the ventrally directed somatosensory pathway is arranged as a cortical hierarchy. An unexpected finding in this study was that, following a postcentral lesion, the SII region undergoes major functional reorganization, in that the SII tissue vacated by the original representation does not remain silent but, instead, becomes occupied by representations of different body parts, providing evidence for a previously unrecognized degree of cortical plasticity in adult primates. Our neurobehavioral evidence indicates that bilateral insular lesions cause a severe tactile recognition deficit, consistent with the suggestion that insularcortex is a critical link in a parieto-insulo-limbic pathway for tactile recognition, and so occupies a position analogous to that of area TE in the occipito-temporo-limbic pathway for visual recognition. These comparisons suggest that sensory-limbic interactions through a hierarchically organized cortical pathway is a mechanism common to memory formation in all sensory modalities.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02036-09 LN

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neural representations of visual stimuli in the extrastriatte cortex

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R. Desimone	Research Psychologist	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	L.G. Ungerleider	Research Psychologist	LN NIMH
	D. Boussaoud	Visiting Fellow	LN NIMH
	L. Lin	Visiting Fellow	LN NIMH
	S.R. Lehky	Guest Researcher	LN NIMH
	C.M. Wessinger	Guest Researcher	LN NIMH

COOPERATING UNITS *(if any)*

Laboratory of Neuropsychology

LAB/BRANCH

SECTION
NIMH, NIH, Bethesda, MD 20892

INSTITUTE AND LOCATION

TOTAL MAN-YEARS: 2.5

PROFESSIONAL: 1.0

OTHER: 1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Disorders of perception, attention, and memory frequently accompany the major mental diseases. To begin to understand the neural mechanisms of these mental processes, we are recording the activity of neurons in the extrastriate cortex of monkeys engaged in tasks requiring visual discrimination, selective attention, and recognition memory. We found that selective attention gates visual processing by (1) filtering unwanted information from the receptive fields of extrastriate neurons, (2) sharpening neuronal selectivity in tasks requiring increased attention, and (3) enhancing neuronal responses when a stimulus must be stored in short-term memory. To identify the mechanisms by which cognitive state modulates cortical activity, we are examining both extrastriate neuronal activity and animal behavior in an attention-demanding task following chemical deactivation of subcortical structures that provide direct or indirect inputs to extrastriate cortex. These studies have identified two structures, the lateral pulvinar and the superior colliculus, that appear to be critical for the ability to focus attention on a single stimulus and ignore distracting stimuli.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02035-09 LN

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Anatomy of the primate visual system

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	L.G. Ungerleider	Research Psychologist	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	R. Desimone	Research Psychologist	LN NIMH
	D. Boussaoud	Visiting Fellow	LN NIMH
	J.S. Baizer	Assoc. Professor	SUNY Buffalo

COOPERATING UNITS (if any)

SUNY Buffalo

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS: 4.0	PROFESSIONAL: 1.0	OTHER: 3.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

To better understand the role of visual association cortex in perception and memory, we have examined the functional areas that comprise this cortex in the macaque and explored their interconnections by the use of neuroanatomical tracing techniques in combination with physiological recording of neural activity. Our results indicate that a multiplicity of separate visual areas lie beyond the striate cortex (V1) in the stream of information processing. These areas are organized into two divergent cortical pathways, each having V1 as the source of its initial input. One, an occipitotemporal pathway, enables the recognition of objects, while the other, an occipitoparietal pathway, mediates the appreciation of spatial relationships among objects as well as the visual guidance of movement. The areas along the occipitotemporal pathway (V1, V2, V3, V4, and TEO and TE of the inferior temporal cortex) appear to be organized as a serial hierarchy, in which each area processes both color and form. By contrast, the areas along the occipitoparietal pathway (V1, MT, and MT's projection zones in parietal cortex) process the direction of stimulus motion. Because a major component of this pathway extends anteriorly within the superior temporal sulcus, the neural mechanisms underlying visuospatial function may be more extensive than previously thought. Data from cerebral blood flow studies indicate the existence in humans, as in monkeys, of two distinct visual processing pathways, although there may be cross-species differences in their anatomical locations. To establish the links of both the occipitotemporal and occipitoparietal pathways with the motor system, we have explored the projections of visual association cortex to the striatum. The targets of these projections are the tail of the caudate nucleus and ventral putamen, which project in turn to the substantia nigra, pars reticulata (SNr) and the globus pallidus (GP). Because of the known inputs of the SNr and GP to the supplementary motor and premotor cortex via the thalamus, the striatum could be a link by which the visual system influences behavior.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02033-12 LN

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Metabolic mapping of sensory and memory systems

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R.C. Saunders	Senior Staff Fellow	CDB NIMH
Others:	M. Mishkin	Chief	LN NIMH
	J.H. Bachevalier	Visiting Associate	LN NIMH
	B. Agranoff	Visiting Scientist	U. of Mich.
	C. Kennedy	Guest Researcher	LCM NIMH
	L. Sokoloff	Chief	LCM NIMH

COOPERATING UNITS *(if any)*
Clinical Disorders Branch, NIMH
Laboratory of Cerebral Metabolism, NIMH
University of Michigan

LAB/BRANCH
Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS: 0.5
PROFESSIONAL: 0.5
OTHER: 0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The cerebral areas related to vision in the rhesus monkey were identified by comparison of metabolic activity in visually stimulated versus visually deafferented cerebral hemispheres. The results allowed delineation of the visual-nonvisual borders of both an occipitotemporal and an occipitoparietal visual pathway and specification of their points of interaction with frontal, limbic, striatal, and diencephalic structures. In addition, it was found that, within the occipitotemporal pathway, the forebrain commissures contribute to the visual activation of area TE only. A 2-deoxyglucose double-label technique has been tested and found to be capable of mapping the metabolic activity in the brain of a single monkey under two experimental conditions. It will be applied to the study of two different types of visual learning in the same subject.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02032-13 LN

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neural coding of visual stimuli

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. J. Richmond	Senior Surgeon	LN NIMH
Others:	T. J. Gawne	Staff Fellow	LN NIMH
	J. M. Watanabe	Hughes Fellow	HHMI
	L. M. Optican	Section Chief	LSR NEI
	J. W. McClurkin	Staff Fellow	LSR NEI
	P. J. Joseph	Engineering contractor	LSR NEI

COOPERATING UNITS *(if any)*
Laboratory of Sensorimotor Research, NEI
Air Force Office of Scientific Research

LAB/BRANCH
Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	2.0	0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

To study the mechanisms underlying visual perception we recorded the activity of ganglion cell fibers, the fibers that send visual information from the retina to the brain, and compared it with the activity of single neurons in the lateral geniculate nucleus and primary visual cortex, the first two extraretinal stages of visual processing, and inferior temporal cortex, the last visual processing station in the cortex. The three sets of neuronal recordings all showed different temporal response patterns to different visual stimulus patterns. When neurons were analyzed as communication channels carrying information about visual stimuli in their responses, the response patterns could only be represented as the sum of several (3-6) simultaneous, independent patterns of activity. These activity patterns were analyzed as a temporal code, and this code was found to contain more information than that conveyed by the response strength, the usual measure of neuronal response. Through application of our information theoretical analysis we have found that the proportion of information carried in the temporal code increases as the information moves farther from the retina within the visual system. Thus, temporal modulation carries a significantly greater proportion of visual information outside of the retina. We have also found that removal of feedback from visual cortex alters stimulus-dependence, and hence the messages, of lateral geniculate neurons. Given that the anatomical basis of this feedback is duplicated throughout the visual system, this strongly suggests that feedback is required for formation of normal stimulus-related messages. We have also found that the messages of sequentially presented pictures are independent when the stimuli are separated by as little as 30 msec, showing that decoding of temporally modulated stimulus-related messages may be easily carried out.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 MH 02404-03 LPP

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders)*
Psychophysiological Investigations of Preattentional and Attentional Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name. title. laboratory. and institute affiliation)*

PI: Bruno J. Anthony, Ph.D. Senior Staff Fellow LPP, NIMH

COOPERATING UNITS *(if any)*
Department of Mental Hygiene, Johns Hopkins School of Hygiene and Public Health; Baltimore City Public Schools

LAB BRANCH
Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.0	1.0	1.0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☒ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type Do not exceed the space provided)*

The goal of this project is to examine dysfunction of preattentive and attentive regulatory mechanisms in children and infants who exhibit disturbance in the modulation of cognitive, affective, and social processes. Actions of these regulatory mechanisms are assessed through examination of steady-state autonomic and central nervous system activity and of the response of these systems to environmental events. Measurement of the blink reflex, heart rate, respiration, and task performance during rest and in response to simple two-stimulus paradigms permit assessment of the integration of different neural systems (sensory, motor and autonomic), preattentive inhibitory and excitatory effects on sensory processing, and different components of attention including intensity, maintenance, breadth (focus or selectivity), and resistance to distraction. Data collection has continued in a study comparing regulatory functioning in groups of 7-to-11-year-olds with Attention-deficit Hyperactivity Disorder (ADHD), with Tourette's Disorder (TD), and with both ADHD and TD.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02295-04 LPP

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Genetic Factors in Response to Alcohol

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Connie C. Duncan, Ph.D.	Research Psychologist	LPP/NIMH
Co-PI:	Frances H. Gabbay, Ph.D.	Guest Researcher	LPP/NIMH
Others:	Allan F. Mirsky, Ph.D.	Chief	LPP/NIMH
	T. Peter Bridge, M.D.	Deputy AIDS Coordinator	ADAMHA

COOPERATING UNITS (if any)
Department of Medical Psychology, Uniformed Services of the Health Sciences

LAB BRANCH
Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The purpose of this project is to assess the relative contributions of genetic and environmental factors to alcohol drinking and response to alcohol challenge. The project is composed of three studies. In the first, male monozygotic (MZ) and dizygotic (DZ) twin pairs complete a 28-day record of their alcohol intake. These data will permit estimation of the relative contributions of genetic and environmental factors to frequency, amount, and pattern of alcohol consumption. In addition, self-reports of contact between cotwins will permit estimation of the importance of shared environment on cotwin similarities in alcohol drinking.

In a second study, electrophysiological and behavioral measures are being employed in a study of drug response. Adult males are tested in two separate sessions using a protocol which consists of electrophysiological measures (e.g., brainstem auditory evoked responses, spectrally analyzed EEG, and visual and auditory event-related potentials), a behavioral measure of attention, self-reports of affect, and a measure of standing stability. Following baseline recording, subjects are administered 0.80 g/kg of 95% ethyl alcohol. This study will permit estimation of the retest stability of the alcohol effects. This information will be critical in the dose-response analysis and in the selection of table measures for a twin study.

In a third study, male MZ and DZ twin pairs receive, in three separate testing sessions, a placebo and two doses of alcohol (0.40 and 0.80 g/kg). The use of placebo and multiple doses of alcohol will permit conclusions about the effects of alcohol on information processing, response production, mood, and motor activity. The protocol will be similar to that used in the study described above. The twin design will provide information on the relative contributions of genetic and environmental factors to variability in these measures in the drug-free state and following response to alcohol challenge.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02288-05 LPP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies on Etiological Factors in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Seymour S. Kety, M.D.	Senior Scientist, NIMH
Others:	Loring Ingraham, Ph.D.	Senior Staff Fellow, LPP, NIMH
	Paul Wender, M.D.	Prof. Psychiatry, Univ. of Utah
	Bjorn Jacobsen, M.D.	Assoc. Prof Psychiatry, Univ. of Copenhagen
	Fini Schulsinger, M.D.	Prof. Psychiatry, Univ of Copenhagen
	Dennis Kinney, Ph.D.	Asst. Prof Psychiatry, Harvard University

COOPERATING UNITS *(if any)*

Psychological Institute, Copenhagen, Denmark; McLean Hospital, Belmont, Mass.; Harvard University; University of Utah.

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Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.0	2.0	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies of the occurrence of mental illness in families have been useful in identifying familial forms of the illnesses and in the development of hypotheses regarding the form and strength of genetic and environmental factors in etiology. Where these major variables are separated by the process of adoption, specific etiologic hypotheses can be tested separately and in combination. In our national register of the nearly 15,000 Danish adoptees who have reached maturity, classical schizophrenia and schizophrenia-like disorders occurred at a significantly elevated rate in the biological relatives of chronic schizophrenic adoptees and not in their adoptive relatives, as reported in the previous annual report. This provides compelling evidence for the significant operation of genetic factors in the etiology of this disorder. The increased prevalence does not differ significantly from that in the natural families of schizophrenics, indicating that the well established familial tendency in this disorder is an expression of genetic factors, and providing hitherto lacking justification for the use of family studies to examine the modes of genetic transmission and to search for genetic linkages in large pedigrees of naturally reared schizophrenics.

The research this year has focused on the final updating of files and analysis of results for publication. This has included as well a comparison of DSM-III diagnoses of schizophrenia and schizotypal personality disorder with a system of global diagnoses based on the descriptions of Bleuler and DSM-II from the point of view of sensitivity and specificity. Considerable effort was devoted to developing a checklist of symptoms relevant to schizophrenia and its marginal syndromes and employing it in describing probands and affected relatives in the adoption sample.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00509-07 LPP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Attention Disorders As Assessed by Brain Event-Related Potentials

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Connie C. Duncan, Ph.D., Research Psychologist, LPP, NIMH

COOPERATING UNITS *(if any)*
Clinical Psychobiology Branch, Neuropsychiatry Branch, Child Psychiatry Branch, Laboratory of Clinical Science, NIMH; Medical Neurology Branch, NINCDS; Chestnut Lodge Hospital; University of Illinois; Johns Hopkins University; Maryland Head Injury Foundation.

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NIMH, ADAMHA, Bethesda, Maryland 20892

INSTITUTE AND LOCATION

TOTAL MAN-YEARS: 2.2	PROFESSIONAL: 3.2	OTHER: 1.0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The aim of this project is to investigate the roles of brain event-related potentials, attention, and information processing and their interrelationships in the etiology, pathology, and prognosis of psychiatric and neurological disorders. Major emphasis is on the diagnostic specificity of disorders of attention and cognition and the identification of the specific aspects or stages of information processing underlying observed decrements in performance. Concurrently recorded brain event-related potentials and performance on cognitive tasks are used to differentiate patterns of dysfunction in attentive mechanisms in subjects with diagnoses of seasonal affective disorder, schizophrenia, seizures, eating disorders, dyslexia, closed head injury, attention deficit with hyperactivity disorder, and Tourette's Disorder. A related objective of this project is to differentiate state versus trait attributes of these disorders to increase understanding of their etiologies. Brain event-related potentials are also used to investigate the role of altered neurochemical mechanisms by comparing drug-induced electrophysiological and behavioral effects with those seen in the various disorders. Correlations between brain event-related potentials and neuroimaging (magnetic resonance imaging) data are used to study the relationship between indices of information processing and the volume of brain regions implicated in the pathophysiology of schizophrenia. Psychological correlates are investigated by relating the data to extensive neuropsychological, psychiatric, and personality measures as well as to performance on behavioral tasks.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 00508-07 LPP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neuropsychological Evaluation of Psychiatric and Neurological Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: Connie C. Duncan, Ph.D., Research Psychologist, LPP, NIMH

COOPERATING UNITS *(if any)*
BPB, NIMH; MNB; MN; NINDS; LN; NIMH; Chestnut Lodge Hospital; Johns Hopkins University; Maryland Head Injury Foundation; Medical College of Pennsylvania; Virginia Commonwealth University; University of Washington; University of Pittsburgh

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INSTITUTE AND LOCATION NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS: 2.5	PROFESSIONAL: 1.0	OTHER: 1.5

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A set of comprehensive neuropsychological test batteries is used to provide a complete assessment of various cognitive and sensory functions that can be related to damage or dysfunction in different regions of the brain. The adult battery comprises tests designed to tap the following aspects of behavior: attention, executive functions, language, memory, motor functions, orientation, selected sensory and perceptual functions, vigilance, and visual-spatial functions. In addition, adults are given a test of general intelligence and a personality inventory. In some studies, subjects are administered a structured psychiatric interview. Modified batteries have been developed for the assessment of infants, preschool children, and children ages 6-16. The data provided by these batteries are being used to construct a neuropsychological theory of the elements of attention that may be applied to the neurological and psychiatric diagnostic groups under study in the LPP. The LPP has as its major focus disorders involving impaired attention, including schizophrenia, seizures, eating disorders, affective disorders, head injuries, and AIDS dementia complex. Comparisons are being carried out between the neuropsychological profiles of various groups of psychiatric patients and those of patients with known cerebral lesions in specified brain regions. Our data are also being used to delineate neurobehaviorally-defined subgroups within diagnostic categories, an undertaking aimed at reducing variability in psychiatric diagnosis, treatment, and outcome. The data provided by this protocol provide a complete behavioral assessment that may be integrated with concurrently gathered electrophysiological, neuroradiological, and biochemical information.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00504-09 LPP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Models in the Monkey of Generalized Seizures of the Absence Type

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Allan F. Mirsky, Ph.D.	Chief	LPP, NIMH
Others:	Eva Bakay Pragay, Ph.D.	Guest Researcher	Munich, West Germany
	Michael Myslobodsky, M.D., Ph.D.	Professor, Univ. of Tel Aviv	Israel
	Richard Coppola, Ph.D.	Engineer	CBD Branch NIMH

COOPERATING UNITS *(if any)*

Tel Aviv University, Israel

LAB BRANCH
Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.7	0.7	0.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Generalized seizure activity with the electrographic appearance of absence epilepsy (bilaterally symmetrical and synchronous paroxysmal three-per-second spike and wave discharges) can be elicited in the monkey by a variety of methods. These include electrical stimulation of various locations within the brain, injection of convulsant drugs and other substances, and administration of compounds which may alter normal inhibitory mechanisms within the cell. Model seizure states created in these ways are studied in order to test hypotheses about pathophysiological seizure mechanisms, sensory processing and attentional capacities during absence seizures, effects of spike-wave activity on cellular activity, and effects of techniques or maneuvers which may modify or reduce convulsive activity. Most recently this project has involved the following work: we studied the behavioral and electrographic effects of a GABA-enhancer and surveyed the attention-related cells in the frontal lobes of the monkey. Other studies of "attention" cells in inferior parietal and preoccipital cortex have been completed as well.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 MH 00503-09 LPP

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Human Clinical Studies of Attention Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Allan F. Mirsky Chief LPP, NIMH

COOPERATING UNITS *(if any)*

Epilepsy Branch, NINCDS; Clinical Neurosciences Branch, NINCDS; Laboratory of Clinical Sciences, NIMH; Neuropsychiatry Branch, NIMH; Boston University

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Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.0	1.25	

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This research comprises three related areas of investigation concerned with specifying neuropsychological factors underlying clinical conditions in humans in which disturbed attention is a major symptom. A major emphasis is on (1) illuminating the nature of brainstem pathophysiology, if any, in such entities as petit mal or absence epilepsy, infantile autism, schizophrenia, and related diseases; (2) an additional major emphasis is on extending the neurobehavioral analysis of attention loss in absence epilepsy so as to facilitate developing alternative treatment strategies for such patients. Both of these projects form part of a larger effort which is aimed at (3) developing a comprehensive and systematic taxonomy of attentional disorders in humans. This latter study will eventually comprise study of patients with cerebral lesions, seizures, demening diseases, and metabolic illnesses of the brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00491-13 LPP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Personality Factors and Psychophysiological Responses to Changing Stimulus Input

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Theodore P. Zahn, Ph.D.	Research Psychologist	LPP, NIMH
Other:	Thomas N. Robinson, Jr.	Guest Researcher	LPP, NIMH

COOPERATING UNITS *(if any)*

NIH Normal Volunteer Office.

LAB BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS 0.2	PROFESSIONAL 0.2	OTHER 0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The objectives of this project are to investigate relationships among differences in personality, sensory thresholds, reaction time, and autonomic nervous system (ANS) activity in normal humans. Bilateral skin conductance and heart rate have been recorded in sessions in which constant and variable intensity tones and lights are presented, in which auditory and two-flash thresholds (TFT) determined by methods which permit signal detection analyses and in which simple reaction time is measured. Several standardized personality tests were also given. These include scales of sensation-seeking, extraversion, neuroticism, psychoticism, field dependence and anxiety. In addition comprehensive measures of lateral dominance have been given. A procedure for manipulating ANS arousal experimentally with minimal distracting effects--a change in posture from supine to standing--was used to study such problems as the effects of base levels on responsivity, the effects of arousal on performance, and the effects of personality variables on this relationship. This project allows testing of several theoretical models of the relationships of ANS activity, sensory sensitivity, and personality, some of which have implications for the etiology of psychopathology. Tests of the relationships between laterality in skin conductance variables and behavioral laterality will also be done to see if inferences about lateralized brain function can be made from such variables.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00486-17 LPP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Psychophysiological Effects of Stimulant Drugs in Children

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Theodore P. Zahn, Ph.D.	Research Psychologist	LPP, DIRP, NIMH
Other:	Judith Rapoport, M.D.	Chief	CHP, NIMH
	Marcus Kruesi, M.D.	Clinical Associate	CHP, NIMH

COOPERATING UNITS *(if any)*

Child Psychiatry Branch, NIMH

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH/ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.6	0.3	0.3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Tests of the effects of acute and chronic administration of caffeine on autonomic nervous system (ANS) functioning have been carried out to evaluate the role of ANS activity in the behavioral and subjective effects of this drug. A test of attention using a reaction time method is included.

The test protocol involves recording peripheral indicators of ANS activity such as skin conductance (SC), heart rate (HR), and skin temperature during a session consisting of a rest period, presentation of a series of simple tones to which no response is required, and the reaction time task. Studies have been carried out on the effects of the acute administration of two doses of caffeine and a placebo in 6-13 year old boys and in men, and a study of chronic (2 week) caffeine intake in children.

The effects of both acute and chronic administration of caffeine were increases in SC indices of arousal but some trends toward decreases in HR. The SC results are consistent with the hypothesis that caffeine can be considered a pharmacologic model for anxiety, but the HR effects suggest the model is imperfect. An acute dose protocol on children with anxiety disorders and controls tested the hypothesis, for which there is evidence in adults, that patients with anxiety disorders are more sensitive to caffeine than controls.

A current study compares ANS activity and attention in boys with diagnoses of Conduct Disorder, Oppositional Defiant Disorder and/or Attention-Deficit Hyperactivity Disorder (ADHD), the so-called "externalizing disorders," selected for their antisocial and disruptive behavior in school and elsewhere.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00484-29-LPP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders.)*

Psychophysiological Responsivity and Behavior in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)*

PI: Theodore P. Zahn, Ph.D. Research Psychologist LPP, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Socio-Environmental Studies, Child Psychiatry Branch, Laboratory of Clinical Science, Neuroscience Branch, Biological Psychiatry Branch, and Clinical Neurogenetics Branch, NIMH.

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.9	0.7	0.2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type Do not exceed the space provided)*

The general purpose of this project is to investigate the roles of autonomic nervous system (ANS) activity, attention, and information processing and their interrelationships in the pathology, etiology, and prognosis of psychiatric disorders. A second purpose is to determine biological and psychological processes related to ANS activity and attention. ANS activity is assessed by peripheral measures, such as skin conductance, heart rate, and skin temperature. Subjects are tested under conditions of rest, presentation of tones, and performance on tasks such as reaction time, mental arithmetic, and memory.

Biological mechanisms are investigated by correlating these variables with enzyme activity, neuropeptides, and levels of biogenic amines and their metabolites and with brain dysfunction as revealed by CT and PET scans.

Studies are being or have been done on unmedicated patients with schizophrenia and several other psychiatric disorders to test the diagnostic specificity of patterns of ANS activity. Children of parents with bipolar affective disorder have been studied to determine possible ANS trait markers. Blood samples are taken during ANS recording in studies of the effects of success and failure to escape an aversive noise, the effects of yohimbine and the effects of stress in patients with premenstrual syndrome. Clinical trials of various treatments are studied in various groups.

Psychological correlates are studied via clinical background data, clinical ratings and questionnaires, and by procedural variations, and by correlations with tests of attention, information processing, and cognition.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00471-34 LPP

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies of Heredity and Environment in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Allan F. Mirsky, Ph.D. Chief LPP, NIMH
Co-PI: Loring J. Ingraham, Ph.D. Senior Staff Fellow LPP, NIMH

COOPERATING UNITS *(if any)*
Oranim Institute for Research on Kibbutz Education, Haifa University, Israel; Hebrew University, Israel; University of Chicago, Illinois

LAB/BRANCH
Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been composed of the following studies: (1) An intensive multi-disciplinary study of a family with MZ quadruplets (daughters) concordant as to schizophrenia but discordant as to severity and outcome; (2) Studies of Danish adoptees and their biological and adoptive families; (3) A study of children (of schizophrenic and control parents) reared in town or kibbutz in Israel. We maintain contact with the quadruplets but have not pursued active studies with them during the past two years. The Danish adoptees are of continuing interest to us and we are preparing additional reports on factors involved in their psychiatric outcome. The Israeli children are the subject of intensive research efforts and we are currently conducting further behavioral and biological studies with them.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00686-01 LSES

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Memory Process in Psychiatrically Impaired Individuals

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: D. Herrmann, Research Psychologist LSES NIMH

COOPERATING UNITS *(if any)*

Cognitive Neuroscience Section, NINCDS, NIH (J. Grafman).

LAB/BRANCH

Laboratorory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.70	0.50	0.20

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project involves the application of research approaches and procedures originally developed for basic research on normal individuals to clinical populations other than schizophrenics. The study examines whether the recall capacity of Alzheimer's patients can improve with practice at retrieving examples of a particular category in a manner analogous to the improvement shown by normals. Also begun is an analysis of the effects of various types of missle head wounds on the memory functioning of injured Vietnam veterans that takes advantage of the LSES's expertise in linear structural equation modeling.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00685-01 LSES

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Memory Processes in Normal Individuals

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: D. Hermann, Research Psychologist LSES NIMH

COOPERATING UNITS *(if any)*

Laboratory of Psychology and Psychpathology, NIH (T. Zahn); Biological Psychology Branch, NIH (H. Weingartner).

LAB/BRANCH

Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.70	0.50	0.20

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study examines the transferability of memory skills and strategies developed doing one memory task to another memory task. Its preliminary findings indicate that if such transfer occurs, it is rare and the amount of transfer generally surprisingly small.

Experiments presently being planned are aimed at finding whether any kinds of effective memory training techniques can be developed. Such research on the transferability of memory skills cannot be divorced from more basic considerations about the nature of memory itself. Also under development is a general theory of memory that incorporates findings not only from the specific field of memory research, but also from social and physiological psychology. In line with this theory, a series of experiments is being carried out on the role of social factors on memory performance and how physiological condition affects memory processes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00684-02

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Representation of Semantic Categories

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: L. Caplan, Staff Fellow LSES NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.30	0.30	0.00

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project involves the development of a model of semantic category representation. Recent experiments demonstrate that the model predicts categorization performance even in individuals, as well as patterns of content effects across different categories and measures of categorization. In addition, another study has investigated similarities and differences in the categorization processes of children and adults.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 00683-02 LSES

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Study of Social and Cognitive Aspects of Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: C. Schooler, Acting Chief, Laboratory of Socio-environmental Studies, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.30	0.30	1.00

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to use the techniques of experimental psychology to investigate the nature of schizophrenics' social and cognitive functioning. One question being addressed is that of the effect of social situations on schizophrenics' performance. This is done in an experiment where schizophrenics perform a perceptual task in which a computer presents stimuli and evalutes response accuracy. Feedback is provided either by the experimenter or by the computer and subjects' responses to the two types of feedback are compared.

Also underway is a study that examines cognitive functioning of schizophrenics by testing their performance in experimental situations in which normally effective cognitive processes actually impair the performance levels of normal individuals. This will be done in order to see whether possible deficits in relevant aspects of schizophrenics' cognitive functioning might permit their performance level to surpass that of normals.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00682-03 LSES

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Environmental Determinants of Cognitive Functioning

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Caplan, Staff Fellow	LSES	NIMH
OTHER:	C. Schooler, Acting Chief	LSES	NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.40	1.00	0.40

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The results of a series of experiments indicate that the effects of analogy in learning a new domain depend on the complexity of the learning experience. Analogies facilitate learning under complex conditions. However, they impair learning under simple conditions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00681-03

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Reciprocal Effects of Self-Esteem and Depression

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: M. Rosenberg, Guest Researcher, Laboratory of Socio-environmental Studies, NIMH

OTHER:	C. Schooler	Acting Chief	LSES	NIMH
	C. Schoenbach	Social Science Analyst	LSES	NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.20	0.10	0.10

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Although low self-esteem has been shown to be associated with a number of non-psychotic disorders among children, adolescents, and adults, the causal connection among these variables has not been established. In order to do so, we plan to make use of a longitudinal data set. This the Youth in Transition study, a five-wave national probability sample of adolescents. Through the use of instrumental variables and structural equation models, we will seek to specify the reciprocal effects of globabl self-esteem and a number of mental health and behavioral variables.

This research has been accepted for publication and the project terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00680-06 LSES

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Work Experiences and the Deinstitutionalized Mentally Ill

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Elliot Liebow, Guest Researcher, LSES, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

X☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The objective of this exploratory, participant observation study is to examine the work experience of the deinstitutionalized mentally ill over time and to seek out ways in which job characteristics, symptoms, and social relationships interact with one another to effect the course of recovery from psychiatric disorder and reintegration into the community. Field work was carried out with residents of halfway houses, participants in community-based psychosocial and transitional work programs, and with "unattached" deinstitutionalized men and women.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00679-09 LSES

PERIOD COVERED

Octobert 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Structural Equation Models in the Analysis of Data with Measurement Error

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Ronald J. Schoenberg, Research Sociologist	LSES	NIMH
OTHER:	C. Schooler, Acting Chief	LSES	NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.40	0.30	0.10

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this work is to further develop the methods and techniques for the specification and estimation of the parameters of structural equation models of survey data that contain random and nonrandom measurement error. Included in this are methods for the identification of the models, estimation of the means of unobserved variables, the determination of model condition, and the treatment of polytomous variables.

Although the work completed is being prepared for publication, because of Dr. Schoenberg's departure for a job in private industry this project will, unfortunately, be terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00672-24 LSES

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Social Psychological Correlates of Occupational Position

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: C. Schooler, Acting Chief, Laboratory of Socio-environmental Studies, NIMH

OTHER:	C. Schoenbach	Social Science Analyst	LSES	NIMH
	M. Kohn	Guest Researcher	LSES	NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.00	1.00	1.00

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
X☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The major accomplishment this year has been the completion of an analysis on how occupational conditions affect the psychological functioning, attitudes and values of Japanese women. Linear structural equation analysis revealed that even in this population, doing self-directed work increases intellectual flexibility.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02458-01 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Not All That Moves is Tardive Dyskinesia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Vikram Khot, M.D., Visiting Associate, Neuropsychiatry Branch, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry

SECTION

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have conducted a review of existing literature which provided age matched prevalence rates for spontaneous and tardive dyskinesia. After conducting a metanalysis we determined the prevalence rates for spontaneous and tardive dyskinesias across various age groups. Our findings suggest that the recorded prevalence of spontaneous dyskinesia after the age of forty is sufficiently high to conclude that many cases which appear to be tardive dyskinesia because of the presence of neuroleptic treatment could actually be attributed to non-neuroleptic causes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02457-01 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuropathologic Studies of Post Mortem Brain of Schizophrenic Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Janice R. Stevens, M.D., Medical Officer, Neuropsychiatry Branch, IRP, NIMH

Dr. Manuel Casanova, Medical Officer, CBDB; IRP, NIMH; Dr. Joel Kleinman, Chief, Section on Neuropathology, CBDB, IRP, NIMH; Dr. Maciej Poltorak, Visiting Scientist, NPB, IRP, NIMH; Dr. Peter Falkai, Univ. Dusseldorf; Dr. Bernard Bogerts Univ. Dusseldorf; Dr. L. Heimer, Univ. Virginia Medical School; Dr. G. Alheid, Univ. Virginia Medical School

COOPERATING UNITS *(if any)*

Clinical Brain Disorders Branch, NIMH; Univ. Dusseldorf, Germany; Univ. of Virginia Medical School, Charlottesville, Virginia

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Aging

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

To search for evidence of anomalous innervation or regeneration in specific nuclei of schizophrenic brains.

NP

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02456-01 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

HLA and Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Robert C. Alexander, M.D., Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. David Daniel, Senior Staff Fellow, Clinical Brain Disorders Branch, IRP, NIMH; Dr. Richard J. Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Clinical Brain Disorders Branch, IRP, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☑ (b) Human tissues ☐ (c) Neither

- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Human leukocyte antigen (HLA) typing was performed on 55 Caucasian schizophrenic patients, who were subdivided into groups on the basis of clinical subtype, response to neuroleptic treatment, enlargement of the lateral ventricles, presence of increased prefrontal and/or parieto-occipital markings, and presence of reversed frontal and/or occipital lobe asymmetry. No observed differences in antigen frequencies between the group as a whole and controls or between any subgroup and the remaining group or controls remained significant after correction for the number of antigens tested.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02455-01 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Anti-HLA Antibodies and Chlorpromazine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Robert C. Alexander, M.D., Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Chlorpromazine (CPZ) has been reported to interfere with the action of alloantibodies directed against human leukocyte antigen (HLA)-A1. We attempted to replicate this finding using peripheral blood lymphocytes from 3 healthy donors in a complement-mediated lymphocytotoxicity assay. We were unable to find evidence of interference between chlorpromazine and the anti-HLA sera tested.

N r

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02454-01 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Molecular and Cellular Studies of the Immune Response in the Laboratory Rabbit

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Henrietta Kulaga, Sr. Staff Fellow, Neuropsychiatry Branch, IRP, NIMH; Dr. David B. Glovinsky, Medical Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Thomas J. Kindt, LIG, NIAID, NIH; Dr. David P. Recker, LIG, NIAID, NIH; Dr. Mary Ellen Truckenmiller, LIG, NIAID, NIH; Dr. Roger Wiggins, University of Michigan; Dr. Thomas M. Folks, RDB, Centers for Disease Control; Dr. Akira Seto, University of Kyoto

COOPERATING UNITS *(if any)*

Laboratory of LIG, NIAID, NIH, Bethesda, Maryland
Dept. of Surgery, University of Michigan
Dept. of Microbiology, University of Kyoto, Japan

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Molecular Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The value of the laboratory rabbit as a model for human retroviruses is being established for studying the processes, prevention and treatment of retroviral diseases. Rabbit cells can be infected in vitro with HTLV-1 and HIV-1. Infection of this species has been confirmed in outbred rabbits in vivo. The present study describes molecular and cellular evidence for HTLV-1 and HIV-1 infection in this system.

N I

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02451-01 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

An Enzyme-Linked Immunosorbent Assay for the Hydra Head Activator Peptide

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David Glovinsky, M.D., Medical Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Henrietta Kulaga, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Hydra Head Activator peptide is a small molecule that plays a key role in the development of the nervous system of the multi celled organism H. Attenuata. Preliminary studies suggest that this 11 amino acid peptide, found in the human brain, may be a potent inducer of nerve cell growth; it is present in key areas of the human brain.

We developed an enzyme-linked immunosorbent assay (ELISA) that quantitatively measures the presence of antibody to Hydra Head activator peptide.

NP

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02450-01 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Screening Human Brain DNA For HTLV-I Proviral Sequences Using PCR Amplification

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David Glovinsky, M.D., Medical Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Henrietta Kulaga, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Robert Alexander, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Darrell Kirch, Medical Director, DIRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Homology between DNA sequences derived from peripheral mononuclear blood cells of patients with multiple sclerosis and the HTLV-I retrovirus have been reported. To extend this inquiry, DNA was extracted from autopsied brains of 10 multiple sclerosis (MS) patients and 10 non-MS controls Attempts to locate DNA sequences that are known to be found in HTLV-I retrovirus were made by applications of the powerful polymerase chain reaction (PCR) amplification technique. Successful amplification of these sequences would add to evidence that this virus is closely associated with, if not causitive, for multiple sclerosis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02420-02 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effect of Chronic Exposure to Cocaine on Metabolism of Catecholamines

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Farouk Karoum, Ph.D., Neurochemist, Neuropsychiatry Branch, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Richard L. Suddath, Medical Staff Fellow, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Molecular Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

  ☐ (a1) Minors

  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cocaine is a habit-forming stimulant that shares with other drugs of abuse the ability to produce rewarding or "reinforcing" effects. Because of the alarming rise in cocaine abuse during the last 15 years, there is a keen interest in cocaine from both public health and basic science perspectives. Various behavior studies imply a major role of central dopamine in the expression of the pharmacological effects of cocaine, but direct biochemical support for this view is at best very sparse and inconsistent. The latter may be attributed to two important factors. First, most reports on the biochemical effects of cocaine were obtained from acute studies. Second, in the majority of these studies, the striatum and nucleus accumbens were the brain regions frequently analyzed. Therefore, certain important brain regions may have been overlooked.

To correct for the above experimental flaws, we have systematically evaluated the effects of 1 to 3 weeks' chronic cocaine administration on central and peripheral biogenic amines, especially the catecholamines. The results of our investigation revealed a preferential, long-term reduction of dopamine turnover and/or metabolism in both the periphery and the brain. In the brain, the frontal cortex and the hypothalamus apparently are the areas most affected.

No further progress has been made on this project as yet.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02418-02 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biologic and Molecular Nature of Putative Neuropathic HIV-1 Isolates

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Rita Anand, Special Expert, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Department of Medical Pathology, University of California, Davis; State University of New York, Stony Brook

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Molecular Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project was transferred to the Laboratory of Biochemical Genetics in December 1988.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02407-02 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Analysis of Growth Factors in Human Cerebrospinal Fluid

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

A. Paul Oliver, Physiologist, Neuropsychiatry Branch, IRP, NIMH

Dr. Richard Suddath, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Anne-Marie Duchemin, Visiting Associate, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH Neuroscience Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have been testing for the presence of growth factors in the cerebral spinal fluid (CSF) of normal and chronic schizophrenic human subjects. The test system uses neurite growth in cells from a neuroblastoma cell line (Neuro 2-A) to assay the presence of growth factors. Indirect growth factors that cause cells to secrete a diffusible growth substance have been demonstrated. Growth factors of unknown composition in CSF have also been demonstrated. However, they are found in normal and schizophrenic subjects with equal probability. Hydra peptide, and somatostatin cause neurite growth but nerve growth factor does not, in this system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02406-02 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Culture of Intact Mammalian Retina

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

A. Paul Oliver, Physiologist, Neuropsychiatry Branch, IRP, NIMH

Dr. Myles J. Jaffe, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. M.A. Von Fricken, George Washington University

COOPERATING UNITS *(if any)*

Department of Ophthalmology, George Washington University, Washington, D.C.

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Aging

INSTITUTE AND LOCATION

NIMH Neurosciences Center at St. Elizabeths, Washington, D.C.

TOTAL MAN-YEARS: 0.4	PROFESSIONAL: 0.3	OTHER: 0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been terminated. A publication has been submitted to the journal Retina.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 MH 02375-03 NPB

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Seasonality of Birth and Hospitalization for Schizophrenic Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Gregory M. Straw, M.D., Medical Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Guido Zani, Ph.D., Saint Elizabeths Hospital

COOPERATING UNITS *(if any)*
Information Systems, Saint Elizabeths Hospital

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Preclinical Neurosciences

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
    ☐ (a1) Minors
    ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Many investigators have reported seasonal variations in the evident birth and admission rates for schizophrenic patients. This project uses computerized hospital records and weather data to elucidate these possible "seasonal" effects.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02374-03 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Clinical Trial of Isotretinoin in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Gregory M. Straw, M.D., Medical Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Darrel G. Kirch, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Myles Jaffe, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Barbara Illowsky, Staff Fellow, Clinical Brain Disorders Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Clinical Brain Disorders Branch, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Preclinical Neurosciences

INSTITUTE AND LOCATION

NIMH Neuroscience Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Open clinical trials of isotretinoin in schizophrenic patients on and off of haloperidol have suggested a possibly beneficial synergism between haloperidol and isotretinoin in treating psychotic illness. This has been supported by the results of animal studies of the direct and synergistic (with haloperidol) effects of isotretinoin on animal behavior. Therefore, this project has been initiated to evaluate these potential effects in a placebo-controlled, double-blind, cross-over study. Also, other possible effects, including changes in visual and auditory sensory processes, will be monitored electrophysiologically.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02313-04 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Retroviral Activity in Lymphocytes of Patients with Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anita Feenstra, Ph.D., Visiting Associate, Neuropsychiatry Branch, IRP, NIMH

Dr. Darrell G. Kirch, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Molecular Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS: 0.5	PROFESSIONAL: 0.5	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

  ☐ (a1) Minors

  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Evidence that schizophrenia may involve infection by a virus (or viruses) has been indirect. The evidence includes the phenomenology of schizophrenia (insofar as it may be mimicked by some viral encephalitides), epidemiological factors (including a predominance among patients with late winter/early spring births, a north-south gradient, and occasional clustering of cases), and indirect laboratory evidence (gliosis in some neuropathological studies, spinal fluid protein abnormalities, and abnormalities in cell-mediated immunity).

The discovery of the human retroviruses (HTLV-I, HTLV-II and HIV, now also known to affect the central nervous system) and the development of new techniques in human retrovirology made it possible to investigate the role of this class of viruses in the etiology of schizophrenia.

Cultures of peripheral lymphocytes of patients with chronic schizophrenia were established and tested for the retrovirus-specific enzyme reverse transcriptase.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE
NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02312-04 NPB

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neurotrophic Activity in Cerebrospinal Fluid of Schizophrenic Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anne-Marie Duchemin, M.D., Guest Researcher, Neuropsychiatry Branch, IRP, NIMH

Dr. Thanh Tam Quach, Visiting Associate, LDN, NICHHD, NIH; Dr. Charles Kaufmann, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Richard Suddath, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*
Laboratory of Developmental Neurobiology, NICHHD, NIH

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Aging

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS: 0.1	PROFESSIONAL: 0.1	OTHER: 0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In a previous study, we found that cerebrospinal fluid of some schizophrenics was able to support survival of sympathetic neurons in culture. This activity was positively correlated with brain ventricle enlargement.

In an attempt to develop an easier assay for the factor responsible for the neurotrophic activity, CSF was tested for neurite-promoting activity on neuroblastoma cells. No correlation was found between the two assays.

No further progress has been made on this project as yet.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

201 MH 02311-04 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Ontogeny and Regional Distribution of Neuropeptide mRNAs in Rodent Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anne-Marie Duchemin, M.D., Guest Researcher, Neuropsychiatry Branch, IRP, NIMH

Dr. Thanh Tam Quach, Visiting Associate, LDN, NICHHD, NIH; Dr. Michael Iadarola, Neurobiology-Anesthesiology Branch, NIDR, NIH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Developmental Neurobiology, NICHHD; Neurobiology-Anesthesiology Branch, NIDR, NIH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.3	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

  ☐ (a1) Minors

  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The project on ontogeny of preprocholecystokinin and proenkephalin has been completed. The same cDNA probes have been used to study the regional distribution of preprocholecystokinin and proenkephalin mRNAs in rodent brain.

The levels of preprocholecystokinin mRNA and cholecystokinin peptide were measured in several regions of rat and mouse brain using RNA blot analysis and radioimmunoassay. Comparison with proenkephalin mRNA levels in the same regions was made.

No further progress has been made on this project as yet.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02282-05 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurovirology and Neuroimmunology of Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Darrel G. Kirch, M.D., Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Robert C. Alexander, M.D., NPB, IRP, NIMH; Dr. David Glovinsky, M.D., NPB, IRP, NIMH; Dr. Nicholas M. Papadopoulos, Clinical Chemistry Service, NIH; Dr. Olivia Preble, NIAID; Dr. John Sninsky, Cetus Corporation; Dr. Steven Spector, University of California at San Diego; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Clinical Chemistry Service, NIH; NIAID; Cetus Corporation; University of California at San Diego

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project on neurovirology and neuroimmunology is focused on obtaining evidence that the pathogenesis of schizophrenia and other neuropsychiatric illnesses may involve an infectious process by a viral agent and/or an autoimmune reaction involving central nervous system tissue autoantibodies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02281-05 NPB

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neural Tissue Microchip Interface

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

A. Paul Oliver, Physiologist, Neuropsychiatry Branch, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Myles Jaffe, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Marty C. Peckerar, Naval Research Laboratory

COOPERATING UNITS *(if any)*

Microelectronics Processing Facility, Naval Research Laboratory, Washington, D.C.

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS: 1.0	PROFESSIONAL: 1.0	OTHER: 0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Development of a neural prosthesis requires fabrication of a solid state device capable of recording information from neural tissue and stimulating it in a timely manner. We began this process by designing a simpler system to test and monitor cultured neural tissue. We identified some problems (such as suitable insulation for the device and corrosion in a critical part of the system) and we improved the tissue culture system to make the tests as realistic as possible. We have also worked with cultured retinal tissue in the system so that two-way communication could be achieved.

No further progress has been made on this project as yet.

IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02263-05 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Haloperidol Pharmacodynamics and Clinical Response in Schizophrenia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Darrell G. Kirch, M.D., Neuropsychiatry Branch, IRP, NIMH

Richard Jed Wyatt, M.D., Chief, NPB, IRP, NIMH; Dr. Richard L. Suddath, NPB, IRP, NIMH; Dr. Llewellyn B. Bigelow, CBDB, IRP, NIMH; Dr. Markku Linnoila, NIAAA; Dr. Greg Gerhardt and Dr. Robert Freedman, University of Colorado; Dr. Neil Benowitz, University of California at San Francisco; Dr. Ian Creese, Rutgers University; Dr. Steven Potkin, University of California at Irvine; Dr. Marc Hertzman, George Washington University

COOPERATING UNITS (if any)

NIAAA, NIH; University of Colorado; University of California at San Francisco; Rutgers University; University of California at Irvine; George Washington University

LAB/BRANCH

Neuropsychiatry

SECTION

Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

As part of a standardized research sequence in the NIMH intramural clinical research program, patients with schizophrenia are withdrawn from neuroleptic medication and, after clinical relapse, treated with a fixed dose of haloperidol. This in turn allows a variety of studies regarding the pharmacokinetics of haloperidol and the effects of haloperidol and other neuroleptics on central nervous system catecholamines. Other pharmacological phenomena being examined in these patients include drug-drug interactions involving haloperidol and several other drugs, including nicotine, caffeine, retinoic acids, and ascorbic acid. The direct effects of nicotine and caffeine on central catecholaminergic neurotransmitter/receptor function are also being studied in both clinical and basic science investigations. A final focus is on elucidating the mechanisms involved in the syndrome of polydipsia-hyponatremia, a potentially lethal problem that is relatively common in schizophrenic patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02262-05 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Electroretinography in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Myles Jaffe, O.D., Ph.D., Guest Researcher, Neuropsychiatry Branch, IRP, NIMH

Gregory Straw, M.D., Guest Researcher, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Aging

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Dark-adapted retinal function can be best characterized using an amplitude versus intensity plot of the data. Further non-linear analysis of these data show, however, that an entire array of complex data can be reduced to 3 simple yet very telling numbers. One number, the slope of the sigmoid-shaped response curve, was shown to correlate highly with both positive symptoms and abnormal involuntary movements in chronic schizophrenic subjects; another link between retinal function and psychiatric disturbance. An additional study showed just how many data points along the response curve were required to generate meaningful data and is referred to as sampling adequacy in non-linear analysis.

Since curve fitting of dark-adapted ERG data proved to be such a powerful technique, we have also begun to characterize a method for curve fitting of light-adapted data. In the first leg of this study, we determined at what levels of background illumination a subject was adequately light-adapted under ganzfeld conditions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02259-05 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Peripheral and Central Catecholamine Turnover in Mental Illnesses

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Farouk Karoum, Ph.D., Neurochemist, Neuropsychiatry Branch, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Psychopharmacology

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Combined gas chromatographic mass spectrometric methods previously developed to assay biogenic amines in various biological media have been employed to assess total body turnover of norepinephrine (sum NE) and dopamine (sum DA) in human subjects and rats. We have also compared changes in these chemicals after a number of pharmacological manipulations in rats. The aim of these animal studies was to gain an insight into how these pharmacological treatments influence brain catecholamines in depression, schizophrenia, and hyperactive children.

(1) Consistent with our 1985 and 1986 Annual Reports, we have continued to gather additional supportive data that suggest a tendency for sum NE to be elevated in major depression. We have also observed a positive correlation between urinary-free cortico and urinary NE and vanilmandelic acid (VMA), a major metabolite of NE in the periphery in humans.
(2) Total body NE and DA turnover were assessed in both hyperactive children and adults after several pharmacological manipulations. The results indicated a correlation between therapeutic benefit and changes in both sum NE and DA irrespective of the direction of change.
(3) The effects of 4 commonly used antidepressant treatments on rat peripheral and central catecholamines were evaluated. A good correlation between the effects of these drugs and sum NE and sum DA in humans and rats was observed. It is suggested that because of this correlation, changes in the rat brain amines observed probably resemble the changes these treatments induce in the human brain. The treatments were chronic zimelidine, desipramine, electroconvulsion, and lithium.
(4) We are currently attempting to reproduce our initial study on DA and NE turnover in schizophrenia and hope to also include patients with tardive dyskinesia.

No further progress has been made on this project as yet.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02257-05 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biochemical and Neuroradiologic Abnormalities in Tardive Dyskinesia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Michael F. Egan, M.D., Medical Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Robert Alexander, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Alison Reeve, Medical Staff Fellow, Clinical Brain Disorders Branch, IRP, NIMH; Dr. Richear Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Clinical Brain Disorders Branch, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	1.4	.4

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We are replicating the results of a preliminary outpatient study in which alpha-tocopherol was found to significantly improve measures of tardive dyskinesia, a disorder seen in patients who have had long-term neuroleptic treatment. The current study is a double-blind, placebo-controlled study using higher doses than the first study and for longer periods. The 8 patients enrolled so far show no adverse reactions. We will examine measures of involuntary movements, neuropsychological functioning, psychopathology, and awareness of presence of abnormal movements before and after treatment. An outpatient clinic has been started to assist in recruiting patients for a new outpatient version of the original protocol.

We are studying 4 hypotheses. First, alpha-tocopherol significantly reduces tardive dyskinesia's severity (as measured by the AIMS rating scale), and this change is not due to fluctuations in medication levels. Second, the disorder is associated with abnormalities on MRI scans, including a higher incidence of enlarged ventricles and cortical sulcal prominence compared to age- and gender-matched psychiatric controls. Third, older patients with the disorder have lower average IQs than matched controls and do significantly worse on neuropsychological tests of striatal functioning; whereas, younger patients are similar to controls. Finally, alpha-tocopherol improves measures of negative symptoms (as mesaured on the NSRS) and awareness of movement disorder (as measured by a self-awareness scale).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02256-03 NPB

PERIOD COVERED

October 1, 1989 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Defect Symptoms in Schizophrenia: Their Measurements, Correlates, and Treatment

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Darrell G. Kirch, M.D., Senior Staff Fellow, NPB, IRP, NIMH; Edward H. Taylor, Ph.D., NPB, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP , NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects
  ☐ (a1) Minors
  ☐ (a2) Interviews
☐ (b) Human tissues
☐ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Renewed interest in the role of negative symptoms in "defect state" schizophrenia encouraged us to develop a "Negative Symptom Rating Scale (NSRS)" to more efficiently measure this syndrome. A study has been conducted performing a factor analysis of the NSRS. Studies are being conducted to explore the relationship between schizophrenia, social intelligence, general intelligence, negative symptoms and premorbid social functioning in schizophrenic patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 MH 02255-05 NPB

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Calcium Channel Inhibitors: Interactions Systems - Human Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Gregory M. Straw, M.D., Medical Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Darrell Kirch, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Llewellyn B. Bigelow, Associate Clinical Director for WAW Division, Saint Elizabeths Hospital; Dr. Edward Taylor, Clinical Social Worker, NPB, IRP, NIMH; Dr. Richard Suddath, Medical Staff Fellow, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Preclinical Neurosciences

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Calcium channel inhibitors (CCI) are thought to affect calcium flux through membrane-bound channels as their major site of action. Reports of clinical trials involving over 150 patients suggest that CCIs also have beneficial effects in neuropsychiatric disorders. Each of the 4 major subclasses of CCIs appears to have unique combinations of biochemical and behavioral properties. Additional studies have suggested a complex interaction between dopamine receptor function and calcium channels. We have completed a study of the clinical effects of verapamil in a schizophrenic population where trends toward improvement did not reach statistical significance. We have proceeded with the protocol to examine the effects of nifedipine in a similar cohort.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02253-05 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Brain Tissue Transplantation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William J. Freed, Ph.D., Chief, Preclinical Neurosciences Section, NPB, IRP NIMH

Dr. Maciej Poltorak, Visiting Associate, NPB, IRP, NIMH; Drs. Herbert Geller and Jeff Laskin, Rutgers University; Dr. Saul Schwarz, Sean Logan, and Dale E. Braun, Naval Hospital; Dr. Gary Simonds, Walter Reed Army Hospital; Dr. Jill Becker, University of Michigan

COOPERATING UNITS *(if any)*

Dept. of Pharmacology, Rutgers University, New Brunswick, NJ; Dept. of Neurosurgery, Naval Hospital, Bethesda, MD; Dept. of Neurosurgery, Walter Reed Hospital, Washington, D.C.; Dept. of Psychology, University of Michigan, Ann Arbor

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Preclinical Neurosciences Section

INSTITUTE AND LOCATION

NIMH Neuroscience Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study is primarily aimed at transplanting tissues containing catecholamines (L-DOPA), including adrenal medulla, tumor cells, genetically altered cells, and embryonic brain tissue, into the brain. Its purpose is to elucidate the properties of these tissues after transplantation and to elucidate the response of the host brain to the transplanted tissues. Specifically, these experiments employ nonprimate animal models to (1) develop the techniques of brain tissue transplantation for clinical use in Parkinson's disease; (2) develop brain tissue transplantation techniques so they eventually may be applicable to other disorders, such as schizophrenia and epilepsy, if and when these disorders become sufficiently understood to permit such applications; and (3) elucidate factors that control brain development and responses of the brain to injury or impairment, with particular emphasis on the nigrostriatal dopamine system. During the past reporting year, significant progress has been made in these areas.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02250-05 NPB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Purification of Messenger RNAs Encoding for Neurotrophic Factors in the Rat Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anne-Marie Duchemin, M.D., Guest Researcher, Neuropsychiatry Branch, IRP, NIMH

Dr. Thanh Tam Quach, Visiting Associate, NICHHD, NIH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Bruce K. Schrier, Laboratory of Developmental Neurobiology, NICHHD, NIH

COOPERATING UNITS *(if any)*

Laboratory of Developmental Neurobiology, NICHHD, NIH, Bethesda, MD.

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS: .60	PROFESSIONAL: .60	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Brain injury is associated with morphological, immunological, and biochemical modifications, some of which may be involved with a healing process. Neurotrophic factors have been shown to appear in the rat brain after lesion. This project intends the molecular cloning of one of the genes encoding for these lesion-induced neurotrophic factors.

A cDNA library has been constructed from a mRNA fraction from lesioned rat brain, which was shown to be capable of inducing neurotrophic activity when injected into Xenopus oocytes.

Screening of the library by differential colony hybridization and by the test of the neurotrophic activity of the fusion protein of the clones has lead to the isolation of several clones. DNA sequencing and analysis of the fusion-protein of these clones is in progress.

No further progress has been made on this project as yet.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01532-11 LBCG

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Regulation of Catecholamine Receptor

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Christopher Hough, Ph.D., Chemist, LPP/NIMH
De-Maw Chaung, Group Chief, LPP/NIMH

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Preclinical Parmacology

SECTION

Group on Receptor Pharmacology

INSTITUTE AND LOCATION

NIMH, Neuroscience Center at St. Elizabeths, Washington D.C.20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The exposure of many types of cells to β-adrenergic agonist, adrenaline, results in eventual loss in sensitivity to the agonist. This is reflected by a loss in numbers of receptors.
We have shown in the rat glioma cell line, C_6, that the loss of receptors is preceded by a loss in receptor mRNA, and that the two receptor subtypes, β_1 and β_2, are differentially down-regulated in this cell line. This down-regulation requires protein synthesis and is probably modulated by a signal other than that of cAMP synthesis. This is underscored by our finding that β-adrenergic receptor mRNA down-regulation occurs in response to antagonists as well as agonists and cannot be induced within the same time frame by cAMP analogues.

We have found that receptor mRNA down-regulation also occurs in response to contact inhibition, a process essential to regulated cell growth.

These findings have important implications for both our understanding of the regulation of catecholamine responsiveness in the central nervous system as well as the knowledge of changes in the brain that can occur as a result of the use of β-adrenergic antagonists in drug therapies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02351-03 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pathology of Selected Central Nervous System Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. M.F. Casanova, Neurologist and Neuropathologist, NIMH

Dr. D. Price, Director Neuropathology Laboratory, Johns Hopkins University, Dr. R. Struble, Assistan Professor of Neuropathology, Johns Hopkins University, Dr. P Whitehouse, Associate Professor, Case Western University, Dr. J. Kleinman, Deputy Director, CBDB-NIMH.

COOPERATING UNITS *(if any)*

Neuropsychiatry Branch, NIMH

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section On Neuropathology Studies

INSTITUTE AND LOCATION

NIMH, Neuroscience Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	3	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02481-01 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Rating Clinical Status in Chronic Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Bryan Berthot, B.A.

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH Neuroscience Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS 1.5	PROFESSIONAL: 1.5	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02480-01 CBDB

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Effects of a Selective D1 Receptor Agonist, SK&F 38393, in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Daniel R. Weinberger, Chief, CBDB, IRP, NIMH

Dr. Joel E. Kleinman, Deputy Chief, CBDB
Dr. Nancy A. Breslin, Senior Staff Fellow, CBDB
Dr. David G. Daniel, Senior Staff Fellow, CBDB

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Brain Disorders Branch

SECTION
Section on Clinical Studies

INSTITUTE AND LOCATION
NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study is designed to determine the clinical efficacy and effects on prefrontal cortical functioning of a selective D1 receptor agonist, SK&F 38393, in schizophrenic patients. Because 20% of schizophrenics respond only minimally to standard neuroleptics, and because "negative symptoms" (apathy, poor social engagement, flat affect, and poor insight) are particularly treatment resistant, new treatment approaches are needed. Work from several areas of study has suggested that the prefrontal cortex is a source of these deficit symptoms, and that it functions abnormally in these patients. Particularly, work in this branch using regional cerebral blood flow (rCBF), SPECT, and acute treatment of schizophrenic patients with dopamine agonists, indicate that schizophrenic patients have impaired prefrontal functioning which may be amenable to treatment with dopamine agonists..

This drug study is aimed both at determining clinical efficacy of SK&F 38393 in treating schizophrenic symptoms and at understanding the biological effects of a D1 agonist on the CNS. Clinical measurements include ratings of general psychiatric symptoms, negative symptoms, and abnormal movements. Biological measurements include collections of CSF and serum, and the use of SPECT with and without frontal cortex activation (Wisconsin Card Sort). Other methods of understanding the drugs effect on the frontal cortex include a neuropsychological battery and use of a social competency instrument.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 MH 02479-01 CBDB

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Acute Amphetamine - Schizophrenic Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Terry Goldberg, Ph.D., Special Expert, CBDB, NIMH

Joel E. Kleinman, M.D., Ph.D., Deputy Chief, CBDB, NIMH; Llewellyn B. Bigelow, M.D., Sen. Staff Scientist, CBDB, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Brain Disorders Branch

SECTION
Section on Clinical Studies; Neuropathology

INSTITUTE AND LOCATION
NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.5	0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The study provided evidence that some schizophrenic patients could benefict from a dopamine agonist (while they were maintained on haloperidol). Thus six of 15 patients appeared quatitatively to improve, possibly because dopamineric reward systems in frontal cortex were stimulated by amphetamine. However, improvements in cognition were not observed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02478-01 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effect of Amphetamine on Cerebral Blood Flow In Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. David G. Daniel, Senior Staff Fellow, CBDB, DIRP, NIMH

Dr. Douglas W. Jones, Physicist, CBDB, DIRP, NIMH; Dr. Richard Coppola, Senior Engineer, CBDB; DIRP, NIMH; Dr. Jeffrey Zigun, Senior Staff Fellow, CBDB, DIRP, NIMH; Dr. Joel E. Kleinman, Deputy Chief, CBDB, DIRP, NIMH; Dr. Terry Goldberg, Neuropsychologist, CBDB, DIRP, NIMH; Dr. Llewellyn Bigelow, Medical Officer, CBDB, DIRP, NIMH; Dr. Karen Faith Berman, Staff Psychiatrist, CBDB, DIRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Neuropathology Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Several lines of evidence suggest a monoaminergic role in the pathophysiology of hypofrontality in schizophrenia. Recently, we observed that apomorphine, a direct dopamine agonist, increased prefrontal cortex (PFC) blood-flow (Xe-133 rCBF) during the Wisconsin Card Sort (WCS), a PFC-linked task. To further explore the role of monoamines on cerebral function we conducted a double-blind placebo controlled cross-over study of the effects of .25 mg/kg dextroamphetamine on cerebral blood flow (CBF) as determined by Xe-133 dynamic performance of the WCS and a simple control task. Subjects included 10 patients with chronic schizophrenia who had been stabilized for six weeks on .4 mg/kg haloperidol.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02477-01 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Anti-HIV Potential of Pentosan Polysulfate

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Llewellyn B. Bigelow, Senior Scientist, CBDB, DIRP, NIMH

Dr. Carl Merril, BGB, DIRP, NIMH; Dr. Rita Anand, BGB, DIRP, NIMH

COOPERATING UNITS *(if any)*

Biochemical Genetics Branch, NIMH

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH Neuroscience Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Pentosan polysulfate (PPS), a semi-synthetic polyanion, has been under Investigation here for a number of years as a prophylactic treatment for migraine and cluster headache. Since we observed an Increase of circulating T-cells In treated patiens and because of the reported synergism of another sulfated polyanion, dextran sulfate, with AZT, we have performed In-vitro experiments to evaluate the therapeutic potential of this drug.

Using human peripheral blood mononuclear cells we have been able to demonstrate synergism of PPS with aziduvine (AZT) in the suppression of HIV-1 growth. We also observed that PPS and dextran sulfate alone in concentrations less than 1.0 μg/ml stimulated viral replication.

This latter finding is particularly important because of the reported "underground market" for dextran sulfate. It suggests that persons with AIDS could actully worsen their condition If they were to take polyanions such as dextran.

On the other hand, the finding of a powerful synergism between AZT and PPS gives encouragement to careful design of clinical research to evaluate this substance as an adjunct to the treatment of AIDS that migh permit effective lower dosing of AZT.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 MH 02476-02 CBDB

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clozapine vs. Haloperidol in Treatment Refractory Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Llewellyn B. Bigelow, Senior Scientist, CBDB, DIRP, NIMH

Dr. Nancy Breslin, Senior Staff Fellow, CBDB, DIRP, NIMH; Dr. Nicholas Carosella, Senior Staff Fellow

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Brain Disorders Branch

SECTION
Section on Clinical Studies; Section on Neuropathology

INSTITUTE AND LOCATION
NIMH Neuroscience Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Clozapine has been called an "atypical neuroleptic" because it does not induce the characteristic elevations in prolactin levels not does it produce the extrapyramidal reactions common to "classical" neuroleptics.

We are conducting a blinded crossover study comparing clinical and biological response of treatment refractory schizophrenics to clozapine versus haloperidol.

When enough patients have been studied we will have clinical, neuropsychological, and SPECT studies of each patient on haloperidol, placebo and clozapine. These results may shed some light on the underlying mechanisms for the often unique clinical responsiveness of patients to clozapine.

To date four patients have begun this 18 week protocol; none have completed it.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02474-01 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders.)*

Evoked Responses Using MEG and EEG

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name, title, laboratory, and institute affiliation)*

Dr. Alison Reeve, Medical Staff Fellow, CBDB, DIRP, NIMH

Dr. Douglas F. Rose, Senior Staff Fellow, MNB, DIRP, NINCDS; Dr. Susumu Sato, Chief, ES, MNB, DIRP, NINCDS; Dr. Daniel R. Weinberger, Chief, CBDB, DIRP, NIMH

COOPERATING UNITS *(if any)*

Medical Neurology Branch, DIRP, NINCDS

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at St. Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type Do not exceed the space provided.)*

The auditory evoked response was studied in normal volunteers and patients with schizophrenia. The 100 msec (N100) response is thought to be processed in primary auditory cortex. Magnetoencephalography (MEG) was used to determine the source of the N100m (magnetic field associated with the N100). This work was accomplished under protocol 88-N-119 and involved collaboration between two branches, one in NINCDS and on in NIMH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02473-01 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Study of the Development of Prefrontal Dopaminergic Responses to Stress in the Rat.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Nancy A. Breslin, Senior Staff Fellow, CBDB

Dr. George Jaskiw, Visiting Associate, CBDB, Dr. Daniel R. Weinberger, Chief, CBDB

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths

TOTAL MAN-YEARS	PROFESSIONAL.	OTHER.
.10	.10	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The dopaminergic system in the prefrontal cortex appears to be involved in the phenomenology, and perhaps the etiology, of schizophrenia. Despite the delayed onset of this disorder in early adulthood, evidence suggests that brain pathology is present earlier, perhaps from birth. An improved understanding of the development of the dopamine system. In the prefrontal cortex is thus critical to the evolution of theoretical models of this illness and improved treatments.

Another, probably related, aspect of schizophrenia is the ability of stress to precipitate exacerbations. Animal work has already shown that the dopamine system of the prefrontal cortex is selectively activated by conditioned stress, suggesting that an impaired system might account for the low stress tolerance of schizophrenic patients. FG 7142, a beta carboline which acts as an Inverse agonists at the benzodiazepine receptor, appears to be anxiogenic in humans and animals and, interestingly, selectively activates dopamine In the prefrontal cortex of the rat.

We have designed a series of studies to increase the understanding of how the dopaminergic stress response changes as an animal matures, using mild food shock and an anxiogenic drug as stressors. When normal functioning of this system is understood, we can then work to create models of the dysfunction which schizophrenic patients exhibit (e.g. through lesioning experiments) and look at how pharmacologic and other treatments might effect this model.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02472-01 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pathology of Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Manuel F. Casanova, Neurologist and Neuropathologist, CBDB, NIMH

Dr. Daniel R. Weinberger, Chief, CBDB, NIMH
Dr. Joel E. Kleinman, Deputy Chief, CBDB, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS: 7	PROFESSIONAL: 5	OTHER: 2 (Technicians)

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Schizophrenia was studied with quantitative anatomical techniques in order to establish clinico-pathological correlates and elucidate pathogenesis.

At present a major loci of pathology has been found in patients with schizophrenia. The same consists of bilateral diminution in the gray matter content of their temporal lobes. This lesion appears to have a multifocal pattern with the medial aspects of the hemispheres affected in the more anterior levels and the superior temporal gyrus affected at posterior levels. Preliminary work has circumscribed the abnormality to the entorhinal cortex especially the more superficial layers, i.e. those receiving dopaminergic Innervation.

In order to perform their studies the authors have introduced techniques of quantitative shape analysis to neuroimaging and developed a computerized technique for the measurement of cellular disarray In microscopy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02441-02 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Brain Density in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. David G. Daniel, Senior Staff Fellow, CBDB, DIRP, NIMH

Dr. Debra Kostianovsky, (Guest worker) CBDB, DIRP, NIMH; Dr. E. Kim, (Guest worker) CBDB, DIRP, NIMH; Dr. Terry Goldberg, Special Expert, CBDB, DIRP, NIMH; Dr. Manuel Casanova, CBDB, DIRP, NIMH; Dr. Joel E. Kleinman, Deputy Chief, CBDB, DIRP, NIMH; Dr. Daniel R. Weinberger, Chief, CBDB, DIRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies; Section on Neuropathology Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS: .33	PROFESSIONAL: .33	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Several previous studies have demonstrated differences in regional brain density (as derived from CT scan attenuation values) between patients with schizophrenia and normal controls. Interpretation of these studies has been hindered by methodological shortcomings such as failure to control for head size, scanner calibration differences and other confounding variables. The present study offered methodological advances over earlier studies by controlling for head size and normalizing the attenuation values for each scan to an internal standard. CT attenuation values in multiple brain regions in 20 patients with chronic schizophrenia were compared with those of 20 age and sex matched controls. No significant differences emerged between the schizophrenics and normal controls. The results confirm the importance of controlling for artifacts in analysis of CT scan attenuation values and raise questions about the validity of regional CT attenuation values in detecting subtle anatomical abnormalities in schizophrenia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02440-2 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Relationship of Occipital Skull Asymmetry to Brain Perenchymal Measures in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. David G. Daniel, Senior Staff Fellow, CBDB, DIRP, NIMH

Dr. Michael S. Myslobodsky, Visiting Scientist, CBDB, DIRP, NIMH; Dr. Richard Coppola, Senior Engineer, CBDB, DIRP, NIMH; Dr. Daniel R. Weinberger, Chief, CBDB, DIRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS: .40	PROFESSIONAL: .40	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02439-02 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Apomorphine and Cerebral Blood Flow in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. David G. Daniel, Senior Staff Fellow, CBDB, DIRP, NIMH

Dr. Karen F. Berman, Staff Psychiatrist, CBDB, DIRP, NIMH; Dr. Ralph Fawcett, Medical Staff Fellow, NPB, DIRP, NIMH; Dr. Daniel R. Weinberger, Chief, CBDB, DIRP, NIMH

COOPERATING UNITS *(if any)*

Neuropsychiatry Branch

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS: .33	PROFESSIONAL: .33	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We conducted a double-blind placebo controlled study of the effects of .005 mg/kg of apomorphine, a direct acting dopamine agonist, on regional cerebral blood flow (Xe-133 rCBF) during a prefrontal cortex activation procedure in six drug-free schizophrenic patients. Following a simple Numbers Matching control task, each subject received either placebo or active apomorphine (SQ) and then performed a prefrontal activation task (Wisconsin Card Sort). In each patient with schizophrenia, apomorphine increased relative prefrontal flow (paired $t = 2.93$, $n = 6$, $p = .03$) during the prefrontal cortex activation procedure. In addition, during the prefrontal activation task patients showed greater increases in relative prefrontal flow compared to the control task with apomorphine than with placebo (paired $t = 3.31$, $n = 6$, $p = .02$). The results suggest that in schizophrenia enhanced prefrontal dopamine increases relative rCBF in the prefrontal cortex, an area implicated by recent cognitive and physiological studies in the pathophysiology of schizophrenia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02438-02 CBDB

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Unimodal vs Bimodal Distribution of Ventricular Size in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. David G. Daniel, Senior Staff Fellow, CBDB, DIRP, NIMH

Dr. Terry Goldberg, Special Expert, CBDB, DIRP, NIMH; Dr. Daniel R. Weinberger, Chief, CBDB, DIRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Brain Disorders Branch

SECTION
Section on Clinical Studies

INSTITUTE AND LOCATION
NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS: .33	PROFESSIONAL: .33	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02437-02CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Hydergine in the Treatment of the Negative Symptoms of Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. David G. Daniel, Senior Staff Fellow, CBDB, DIRP, NIMH

Dr. Craig N. Karson, Staff Psychiatrist, CBDB, DIRP, NIMH; Dr. Darrell G. Kirch, Medical Director, Neuropsychiatric Research Hospital, NIMH; Dr. Daniel R. Weinberger, Chief, CBDB, DIRP, NIMH

COOPERATING UNITS *(if any)*

Neuropsychiatric Research Hospital

LAB/BRANCH

Clinical Brain Disorders Branch; Neuropsychiatric Research Hospital

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has now been completed and is in the data analysis stage.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02436-02 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Combined Sinemet and Neuroleptic Treatment In Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. David G. Daniel, Senior Staff Fellow, CBDB, DIRP, NIMH

Dr. Joel E. Kleinman, Deputy Chief, CBDB, DIRP, NIMH; Dr. Daniel R. Weinberger, Chief, CBDB, DIRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies; Section on Neuropathology Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS: .33	PROFESSIONAL: .33	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This protocol has been approved by the NIMH ICRS. In order to study the effects of augmenting central dopamine activity on brain function and "negative" or "deficit" symptoms in patients with schizophrenia, we have designed a double-blind placebo-controlled crossover trial of combined l-Dopa and molindone or haloperidol, lasting 16 weeks. Throughout the study patients will receive daily BPRS ratings, and twice weekly NSRS and AIMS ratings. At equivalent times during the active and placebo periods patients will undergo measurement of serum prolactin and growth hormone levels, lumbar puncture, computerized brain electrical activity measurement, and cerebral blood flow measurement either by SPECT or rCBF.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02435-02 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Performance of Chronic Schizophrenic Patients on the Chapman Scales

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Terry Goldberg, Ph.D., Special Expert, CBDB, NIMH

Jim Gold, Ph.D., Psychologist; Daniel R. Weinberger, M.D., Chief, CBDB, NIMH

COOPERATING UNITS *(if any)*

Clinical Services Branch

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies; Clinical Services

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.10	.10	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

  ☐ (a1) Minors

  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Ways to measure psychopathology in schizophrenia are numerous. However, the relation of these symptoms to other variables of interest (namely, brain images and neuropsychological performances) has been somewhat disappointing. Therefore, it is important to search for an inventory of symptoms, attitudes, beliefs, and feelings that might, in fact, be linked to neuropsychological deficit and neuroanatomic or neurophysiologic abnormality. The Chapman/Scales of social anhedonia, physical anhedonia, perceptual aberration, magical ideation, and non-conformity, have been carefully structured and assess symptoms often associated with defect states and symptoms associated with florid psychotic states. The scales were designed so that there is a continuum in distribution between normal subjects, psychotic prone subjects, and schizophrenic patients. As such, they may be relatively sensitive to degrees of psychopathology in important areas of functioning. These may, in some way, be associated with areas of deficit in neuropsychology or neuroanatomy. Moreover, they may be used to subtype patients a more fine grained matter than the typical positive-negative way.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02434-02 CBDB

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neuropsychological Test Findings and MRIs: A Correlative Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Terry Goldberg, Ph.D., Special Expert, CBDB, NIMH

Richard Suddath, M.D., Sen. Staff Fellow, NPB, NIMH; Manuel F. Casanova, M.D., Medical Officer, CBDB, NIMH; Daniel R. Weinberger, M.D., Chief, CBDB, NIMH

COOPERATING UNITS *(if any)*
Neuropsychiatry Branch, NIMH

LAB/BRANCH
Clinical Brain Disorders Branch

SECTION
Section on Clinical Studies; Clinical Neuropsychiatry, Neuropathology

INSTITUTE AND LOCATION
Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS	PROFESSIONAL:	OTHER.
.15	.15	0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
 ☐ (a1) Minors
 ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Computerized image analysis of MRIs has proved to be a valid method of assessing volume in vivo of selected brain structures. The use of one such system (LOATS) enables one to determine the size of such structures as frontal lobe, temporal lobe, caudate, thalamus, and corpus callosum in various coronal and sagittal plains through the use of an edge finding function. In addition, gray matter can be distinguished from white matter and the ventricular system size can be delineated. These measurements can, in turn, be correlated with performance on various neuropsychological measures including Verbal IQ, Performance IQ, Wechsler Memory Scale MQ and Halstead-Reitan average impairment rating. Volumetric reductions in specific brain areas may, in fact, be associated with focal neuropsychological deficits.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02401-02 CBDB

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neuropsychology of Twins

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

E. Fuller Torrey, M.D.

Terry Goldberg, Ph.D., Special Expert, CBDB, NIMH

COOPERATING UNITS *(if any)*
Twin Studies Unit

LAB/BRANCH
Clinical Brain Disorders Branch

SECTION
Section on Clinical Studies

INSTITUTE AND LOCATION
NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The neuropsychological study of twins with psychiatric disorders has rarely been attempted. In the present study, groups of monozygotic twins whose members are both normal, whose members are both schizophrenic, and whose members are discordant for schizophrenia (i.e., one member is normal and one member is schizophrenic) will be assessed with a complete neuropsychological battery. Included tasks that assess motor functioning, attentional skills, memory abilities, higher level abstract problem solving, and basic language and visual spatial functions. Also tests of dichotic listening with both neutral and affectively charged words were administered to assess laterality and emotional responsivity. By the use of matched pair design in which both genetic and early social environment is more or less completely controlled, as well as the experience of twinship itself, it is hoped that the pattern of deficits found will elucidate impairment in schizophrenic disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02399-04 CBDB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Postmortem Brain Tissue Examination In Neuropsychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Joel E. Kleinman, M.D., Ph.D., Deputy Chief, CBDB, IRP, NIMH

Manuel F. Casanova, M.D., Neuropathologist, CBDB; George Jaskiw, M.D., Staff Psychiatrist CBDB; William J. Freed, Ph.D., Section Chief, NPB, IRP, NIMH; Charles A. Kaufmann, Staff Psychiatrist, Dept. of Psychiatry, University of Columbia Medical School; Lori L. Altshuler, Staff Psychiatrist, Biological Psychiatry Branch, IRP, NIMH; Earl B. DeSouza, Section Chief, Neuroscience Branch, NIDA, Bhaskar Kolachana, Ph.D., CBDB; Marc Laurelle, M.D., CBDB

COOPERATING UNITS *(if any)*

NPB, NIMH, NSB, NIDA, BPB, NIMH

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Neuropathology

INSTITUTE AND LOCATION

NIMH, Neuroscience Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7	5	2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

  ☐ (a1) Minors

  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Postmortem studies in neuropsychiatric disorders test hypotheses with regard to schizophrenia, suicide, and addictions. New findings in schizophrenia include the following: (1) decreased width of the parahippocampal gyrus in schizophrenics versus controls; (2) decreased temporal cortex sigma receptors in schizophrenics versus controls with normal PCP receptors; and (3) differences in monoclonal antibodies between schizophrenics and controls.

New findings in suicide studies included decreased width of the right parahippocampal gyrus relative to normal controls.

Lastly, hippocampal glutamate binding was increased in alcoholic brains as compared with controls. This increase was especially pronounced in alcoholics who died from seizures secondary to alcohol withdrawal.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02398-03 CBDB

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Development of an Auditory Sort Test

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Terry Goldberg, Ph.D., Special Expert, CBDB, NIMH

Daniel Weinberger, M.D., Chief, CBDB, NIMH; Craig Karson, M.D., Staff Psychiatrist, CBDB, NIMH; Karen F. Berman, M.D., Staff Psychiatrist, CBDB, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Brain Disorders Branch

SECTION
Section on Clinical Studies

INSTITUTE AND LOCATION
NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS: .35	PROFESSIONAL: .35	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Concepts formation tasks with a set shifting component have proven sensitive to frontal lobe dysfunction. The Wisconsin Card Sort, perhaps the most widely known test of this class, activates prefontal regions in most normal but no schizophrenic subjects. It is presented in the visual modality. We are attempting to develop a task that requires formally similar cognitive operations, but whose stimulus modality differs from the Card Sort (i.e., the test will be auditory). To futher validate the use of such a test and to facilitate cognitive activation in EEG- BEAM studies while reducing eye movement, an auditory analog of the Card Sort was developed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02395-03

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Structural Brain Imaging In Schizophrenic Patients and Normal Subjects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Daniel R. Weinberger, M.D., Chief, CBDB, Branch, NPB, IRP, NIMH

David G. Daniel, M.D., CBDB; George Jaskiw, M.D., Visiting Associate, CBDB, NIMH; Barbara Illowsky, M.D., Medical Staff Fellow, CBDB, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	1	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The projects on structural brain imaging investigates structural pathology of the brains of schizophrenic patients housed in the William A. White research units using x-ray computerized tomography (CT) . Patients are compared to matched normal controls. The most recent study, a culmination of four years of data collection, compared 73 schizophrenic patients to 30 normal volunteer controls. This project is a replication and extension of the previous work done in this area in the branch. Using standardized techniques four brain areas were examined: Lateral ventricles, third ventricles, cortical (parieto-occipital) areas, and prefrontal cortex. In this sample, the lateral and third ventricles continued to be significantly larger in patients than controls. A potentially exciting new finding was that though there were essentially no differences between patients and controls in cortical atrophy in the parieto occipital distribution, the schizophrenic patients showed substantially greater atrophy in the prefrontal distribution, localizing the cortical changes to this area. Further, in a subgroup of 18 drug-free and 22 medicated patients, the CT abnormalities were correlated with regional cerebral blood flow (rCBF) using the radioactive 133 Xenon inhalation technique. Relationships were found between the neurophysiological measurements and CT scanning, especially in the prefrontal cortex and ventricular areas. This work is being amplified to search for clinical and biological correlations of ventricular enlargement and prefrontal atrophy, particularly wiith respect to other signs of prefrontal pathology, e.g. rCBF, EEG, PET data. In addition, we followed up earlier patients, rescanning them after 9-9 years. We have found no change over time, indicating that the pathology underlying these changes probably static.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02434-02 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Magnetic Resonance Imaging (MRI) Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Daniel R. Weinberger, M.D., Chief, CBDB, NIMH

Richard Suddath, M.D., Medical Staff Fellow, NPB, NIMH; John Kelsoe, M.D., Medical Staff Fellow, Clinical, CNB, NIMH; David Pickar, M.D., Chief, Section on Clinical Studies, CNB, NIMH; Manual Casanova, M.D., CBDB, George Christison, M.D., Terry Goldberg, Ph.D., Fuller Torrey, M.D.

COOPERATING UNITS *(if any)*

Section on Clinical Studies, CNB, NIMH

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS: 3	PROFESSIONAL: 1	OTHER: 1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We are studying the neuroanatomical localization of the possibe underlying pathology using MRI. Attempts will be made to correlate neuroanatomical abnormalities to other findings such as those seen in blood flow or BEAM studies. These studies are using state of the arts digitized image analysis system to examine gray-white matter quantitative differences between schizophrenic and normal. Preliminary results indicate that patients have larger ventricles and less temporal gray matter. This represents potentially important evidence of a relatively focal pathological process.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02393-04 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Demeclocycine In The Treatment Of Psychogenic Polydipsia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Barbara P. Illowsky, M.D., Medical Staff Fellow, Clinical Brain Disorders Branch, NIMH

George Christison, M.D., Staff Fellow, Clinical Brain Disorders Branch, NIMH; Darrell G. Kirch, M.D., Senior Staff Fellow, NPB,DIRP,NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section On Neuropathology Studies

INSTITUTE AND LOCATION

NIMH, Neuroscience Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS: 6	PROFESSIONAL: 3	OTHER: 1

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been transferred to NPB project number Z01 MH 02263-05.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02392-03 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Evaluation Of Patients With Prefrontal Leukotomies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Karen Faith Berman, M.D., Staff Psychiatrist, Clinical Brain Disorders Branch, IRP, NIMH; Barbara P. Illowsky, M.D., Medical Staff Fellow, Clinical Brain Disorders Branch IRP, NIMH; Daniel R. Weinberger, M.D., Chief, Clinical Brain Bisorders Branch

Denise Juliano, MSW, Social Worker, Clinical Services Branch, WAW Division
Richard Suddath, M.D., Medical Staff Fellow, NPB,DIRP,NIMH; Terry E. Goldberg, Ph.D., Special Expert, CBDB,IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section On Clinical Studies

INSTITUTE AND LOCATION

NIMH, Neuroscience Center at Saint Elizabeths

TOTAL MAN-YEARS: 10	PROFESSIONAL: 6	OTHER: 2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Prefrontal lobotomies for psychiatric illness were last performed in the 1950's. Approximately 40 patients who had dorsolateral prefrontal lobotomies remain on the patient rolls at St. Elizabeths Hospital. The long-term effects of prefrontal lobotomy and the overall outcome of the patients is not clearly known. Techniques are now available to study anatomic, clinical and physiological aspects of lobotomy patients. These include computerized tomography scanning (CT), magnetic resonance imaging (MRI), and cerebral blood flow (CBF) examination. Neurological, psychiatric, and psychological evaluation of these patients in correlation with the above examinations compared to age and diagnosis-matched non-lobotomized patients and to age-matched normals, will give information on both the effects of prefrontal lobotomy and on the function of prefrontal cortex.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02388-03 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regional Cerebral Blood Flow in Neuropsychiatric Patients and in Normal Subjects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Daniel R. Weinberger, Chief, CBDB, DIRP, NIMH

Dr. Karen Faith Berman, Staff Psychiatrist, CBDB, DIRP, NIMH; Dr. Douglas Jones, Physicist, CBDB, DIRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at St. Elizabeths, Washington, D.C.

TOTAL MAN-YEARS: 4.25	PROFESSIONAL: 2.25	OTHER: 2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We are studying the neuroanatomical localization of the possible underlying pathology of schizophrenia using MRI. Attempts will be made to correlate neuroanatomical abnormalities to other findings such as those seen in blood flow, neurochemistry, or computerized EEG. These studies are using state of the art digitized image analysis system to examine gray-white matter quantitative differences between patients with schizophrenia and normal controls. Our results indicate that patients have larger lateral cerebral ventricles and less temporal lobe gray matter, particularly in the area of the temporal lobe containing the anterior hippocampus. This represents potentially important evidence of a relatively focal pathological process.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02360-03 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Topographic Analysis of Brain Activity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Richard Coppola, D.Sc., Sen. Engineer, CBDB, NIMH

Terry Goldberg, Ph.D., Special Expert, CBDB, NIMH; Alison Reeve, M.D., Med. Staff Fellow, CBDB, NIMH; Daniel R. Weinberger, M.D., Chief, CBDB, NIMH; Francis Newman, Visiting Scientist, BPB; Trey Sunderland, M.D., Med. Officer, LCS, NIMH; Judith M. Rumsey, Ph.D., Sen. Staff Fellow, CPB, NIMH; Harold Sackheim, Ph.D., Columbia University, New York; Richard D. Weiner, M.D., Ph.D., VA, Duke University, N.C.; Werner Herrman, M.D., FU, Berlin, W. Germany.

COOPERATING UNITS *(if any)*

LNP, NIMH; LCM, NIMH; NSB, NIMH; BPB, NIMH; LCS, NIAAA; CPB; LNS, NIA; Columbia University, NY; VA, Duke University, N.C.; FU, Berlin, W. Germany

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	1.5

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

- ☒ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Electrical brain activity, as an index of central nervous system function, is studied across a range of patient groups with neurological and psychiatric disorders as well as normal volunteers. Using electrophysiological data quantified from event-related potentials and spectrum analysis of EEG recordings, computer-derived brain images are able to provide information about neurophysiological function relating to both cognition and clinical state. Topographic maps efficiently characterize spatial and temporal patterns of brain activity allowing the ability to study the dynamic interaction among brain regions and their relation to function.

The project has two main purposes. The first is to refine the topographic and quantitative analysis methods and establish normative data for various conditions and activation procedures. For example, normal subjects differ with respect to their major focus of resting EEG alpha rhythm; one group shows a dominant parietal locus and one an occipital locus, depending on the alpha frequency.

The second purpose is to apply these methods to the characterization of clinical groups and pharmacological response. Work in progress includes characterization of subgroups of Alzheimer's patients, localization of abnormality in epilepsy patients, localization of drug activation and study of psychiatric patients on various neuroleptic drugs..

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02356-03 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Procedural and Problem Solving Abilities in Schizophrenic Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Terry Goldberg, Ph.D., Special Expert, CBDB, NIMH

Jean St.-Cyr, Ph.D., Visiting Scientist, Neuropsychology IRP, NIMH; Daniel R. Weinberger, M.D., Chief, CBDB, NIMH

COOPERATING UNITS *(if any)*

Neuropsychology Laboratory, NIMH

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS: .25	PROFESSIONAL: .25	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02355-03 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Autism: A Study of Cerebrophysiology, Neuroanatomy and Neuropsychology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Terry Goldberg, Ph.D., Special Expert, CBDB, NIMH

Daniel R. Weinberger, M.D., Chief, CBDB, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.5	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02354-03 CBDB

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders.)*

Amphetamine and Frontal Lobe Functioning in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Terry Goldberg, Ph.D., Special Expert, CBDB, NIMH

Joel E. Kleinman, M.D., Ph.D., Deputy Chief, CBDB, NIMH; Llewellyn B. Bigelow, M.D., Sen. Staff Scientist, CBDB, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies; Neuropathology

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS: .25	PROFESSIONAL: .25	OTHER: 0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project was terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02352-03 CBDB

PERIOD COVERED

October 1, 1988 thriugh September 30, 1989

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)

Prefrontal Cortical Modulation of Subcortical Dopamine Systems

PRINCIPAL INVESTIGATOR (*List other professional personnel below the Principal Investigator.*) (*Name, title, laboratory, and institute affiliation*)

Dr. George Jaskiw, CBDB, NIMH

Dr. Bhaskar Kolachana, CBDB, NIMH; Dr. Barbara Lipska, CBDB, NIMH; Dr. Farouk Karoum, NPB, NIMH; Dr. Daniel R. Weinberger, CBDB, NIMH

COOPERATING UNITS (*if any*)

Neuropsychiatry Branch, NIMH

LAB/BRANCH

Clinical Brain Disorders Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH Neurosciences Center at Saint Elizabeths, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.5	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK (*Use standard unreduced type. Do not exceed the space provided.*)

We have continued our investigation into the relationship between cortical and subcortical systems, particularly between catecholamines in the prefrontal cortex (PFC) and the nucleus accumbens and corpus striatum. In studies involving lesions of the medial prefrontal cortex we have focused on the ability of different types of stressors to alter both dopamine linked behaviors and biochemical indices of dopamine function, at a time (more than 6 weeks postoperatively) when baseline indices are not different between sham and lesioned animals.

A variety of pharmacological and environmental stressors appear to attenuate locomotor exploration of a novel environment in rats with frontal lesions. Moreover, the lesion appears to alter the biochemical response of dopamine systems to mild chronic stress. One week following termination of a 7 day series of daily vehicle injections, rats with frontal lesions show enhancement of presynaptic dopaminergic indices in the nucleus accumbens.

Administration of D1 and D2 agonists and antagonists suggest an upregulation of striatal and accumbal dopamine receptors endures several months following frontal lesions.

In conclusion, the prefrontal cortex clearly influences catecholamine turnover and associated behaviors in subcortical areas and this influence becomes particularly important under stressful conditions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02396-02 LCB

PERIOD COVERED
October 1, 1987 through September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Mechanical, Thermal and Optical Signs of Excitation in the Nervous System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Ichiji Tasaki	Chief, Unit on Neurobiology	LCB, NIMH
Others:	Paul M. Byrne	Biomedical Eng. Technician	LCB, NIMH
	Michio Masumura	Visiting Fellow (appt. terminated 12/87)	LCB, NIMH
	Nobuko Tasaki	Guest Researcher	LCB, NIMH

COOPERATING UNITS *(if any)*

LNN, NICHHD; LNC, NINCDS

LAB/BRANCH
Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	1.5	1.5

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

During the past year, further investigations were conducted into the process of water movement and of energy transduction in the nervous system by measuring mechanical and thermal changes during excitation and inhibition. Continuous efforts were made to improve the sensitivity and the time-resolution of the detectors (devised and fabricated in this laboratory) employed in these investigations. Attempts were also made at constructing new types of detectors for measuring rapid mechanical, thermal and optical changes in the nervous system.

Significant achievements made during the past year include (1) elucidation of the process of nerve excitation and conduction in the garfish olfactory nerve by measuring both swelling and heat production during excitation, (2) analysis of the secretory process in the guinea pig pituitary gland by taking mechanical changes in the gland as an index, (3) studies of the mechanism of synaptic transmission in the cervical sympathetic ganglion of the guinea pig, and (4) demonstration of heat production of an unusually great magnitude evoked in the orthodromically activated olfactory bulb (bullfrog) in association with triphasic mechanical changes (swelling-shrinkage-swelling). All these studies are either already completed or near completion. It was repeatedly demonstrated in these studies that the method of recording non-electrical signs of nerve excitation and of synaptic transmission and inhibition reveals important properties of the nervous system which are inaccessible to conventional electrophysiological methods.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02387-02 LCB

PERIOD COVERED

October 1, 1987 through September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Structural Analysis of the CD4/HIV Ligand/Receptor Dyad

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Lee E. Eiden Chief, Unit on Molecular and Cellular Neurobiology, LCB,NIMH

See Attached

COOPERATING UNITS *(if any)*

Genelabs, Inc.; Frederick Cancer Research Facility; Litton Bionetics;
Delta Regional Primate Cntr.; Sidney-Farber Cancer Institute

LAB/BRANCH

Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
6		

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A semi-purified peptide mixture consisting in benzylated derivatives of the CD4-derived peptide TYICEVEDQKEE has been further characterized as an HIV anti-infective, anti-cytopathic and virustatic agent in vitro, at a nominal concentration if 18-32μM. Purified and fully characterized derivatives of TYICEVEDQKEE have been identified which are anti-infective and anti-cytopathic at 40-80μM, but are less potent virustatic agents. One if these has been synthesized in large-scale (10-20 gm), partially purified and characterized, and will be injected into three rhesus macaque monkeys inoculated with the simian immunodeficiency virus B670 as a preliminary test of its anti-viral efficacy and safety in primates in vivo.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00942-08 LGCB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biochemical Reactions in Mammalian Cell Chemotaxis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	R.R. Aksamit	Research Chemist	LGCB	NIMH
	P.S. Backlund, Jr.	Research Chemist	LGCB	NIMH
	G.L. Cantoni	Chief, Laboratory of General and Comparative Biochemistry	LGCB	NIMH

COOPERATING UNITS *(if any)*

Office of Biologics, FDA; Molecular Pathophysiology Section, NIDDK;
Department of Biochemistry and Pharmacology, University of Glasgow, Scotland

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Proteins

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL:	OTHER:
1	1	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Studies in this laboratory have demonstrated a role for methylation in chemotaxis and other important biological responses. In addition, protein synthesis is required for normal, sustained chemotaxis by the RAW264 macrophage cell line. One of the proteins involved in chemotactic signal transduction has been identified as G_i-2 based upon the inhibition of chemotaxis by pertussin toxin and upon the distribution of G_i-2. G_i-2 is the major pertussis toxin substrate in RAW264 cells and is present in another chemotactic cell, the human neutrophil. We have now found that the gamma subunit of G_i is carboxymethylated, a finding that clearly implies a regulatory role for methylation in signal transduction.

The carboxymethylation of a class of GTP-binding proteins distinct from the G_s or G_i families has also been found. The methylated proteins have molecular weights between 20,000 and 23,000 and are found in the membranes of RAW264 cells, rat brain, rat liver, and human buffy-coat cells. Immunochemical experiments indicated that the major methylated proteins in the molecular weight range are not related to ras. It is probable that these proteins play an important role in the regulation of specific cellular receptor systems. The methylation reactions also provide a method to identify and quantitate the methylated proteins.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 MH 02386-02 LCB

PERIOD COVERED
October 1, 1987 through September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neuropeptide Secretion, Synthesis and Action in Neural, Endocrine and Immune Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Lee E. Eiden Chief, Unit on Molecular and Cellular Neurobiology, LCB, NIMH

See Attached

COOPERATING UNITS *(if any)*
U-44 INSERM, Centre de Neurochimie du CNRS, Strasbourg, France; VA Hospital, Washington, DC; LDN, NICHHD; USUHS; Dept. Pathology, U Penn Med Ctr

LAB/BRANCH
Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
6		

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We are examining the molecular mechanisms of neuropeptide secretion, neuropeptide expression and biosynthesis and neuropeptide interactions with their receptors in the developing and mature neuroendocrine system. We are attempting to understand the structural features of peptides and proteins that confer molecular specificity on these three processes. We hope to characterize and develop pharmacological agents that mimick this specificity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02385-02 LCB

PERIOD COVERED

October 1, 1987 through September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Genetic Control of Cell Differentiation, Growth and Transformation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. Okayama	Visiting Scientist	LCB, NIMH
Others:	M. Eiden	Guest Researcher	LCB, NIMH
	A. Masuda	Visiting Fellow	LCB, NIMH
	K. Okazaki	Visiting Fellow	LCB, NIMH
	N. Okazaki	Guest Researcher	LCB, NIMH
	R. Toyama	Visiting Fellow	LCB, NIMH
	T. Yamashita	Visiting Associate	LCB, NIMH
	C. Chen	Biologist	LCB, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.4		

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Mutant NRK cells that are no longer sensitive to TGF-β and EGF have been generated and isolated. These will be used to study the role of TGF-β in malignant transformation.

A cDNA has been isolated that causes chemically transformed Baby Hamster Kidney (BHK) cells to revert to normal phenotype. The mode of action of this recessive oncogene will now be investigated.

A highly efficient technique for transfecting the yeast, schzosaccharomyces pombe has been developed. The method will be used to clone cDNAs that complement mutant yeast that have defective cell cycles, DNA repair mechanisms, etc.

Recombinant viruses have been generated capable of infecting cells but not of replicating within them. These can safely and conveniently be used to study the interaction between viruses and their receptors. In addition, the recombinant viruses may be an efficient means of introducing cloned genes into infectable cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00434-07 LCB

PERIOD COVERED

Octobert 1, 1987 through September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Molecular Mechanisms of Receptor-Mediated Signal Transduction

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Julius Axelrod	Guest Researcher	LCB, NIMH
Others:	R. Burch	Guest Researcher	LCB, NIMH
	B. Conklin	Guest Researcher	LCB, NIMH
	C. Felder	Staff Fellow	LCB, NIMH
	C. L. Jelsema	Guest Researcher	LCB, NIMH
	A. L. Ma	Biologist	LCB, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	5.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Interleukin-1 (IL-2) stimulated the release of PGE_2 in Swiss 3T3 cells. Pretreatment of the cells with IL-2 enhanced the bradykinin stimulated release of PGE_2 10 fold. Similar enhancement was seen for bombesin and thrombin IL-2 induced phospholipase A_2 cyclooxygenase, and GTPase but did not alter receptor number or affinity. Diacyglycerol also stimulated phospholipase A_2 activity in the Swiss 3T3 cells. Unique bradykinin receptors unlike the previously described B_1 and B_2 classification were pharmacologically identified using several bradykinin analogs. These receptors were further characterized according to their differential coupling to phospholipase-C and phospholipase A_2 signal transduction systems. Muscarinic receptors m_1, m_3 and m_5 transfected into fibroblasts stimulated arachidonic acid release, inositolphospholipid turnover and cAMP accumulation., Muscarinic receptors m_2 and m_4 caused a decrease in cAMP accumulation. The receptor mediated release of arachidonic acid was distinct from inositolphospholipid turnover. PMA and carbachol caused a synergistic stimulation of arachidonic acid release, but PMA inhibited inositolphospholipid turnover.Dopamine-1 receptors stimulated inositolphospholipid turnover in renal cortical plasma membranes. This stimulation was independent of adenylate cyclase activity and appear to be linked to phospholipase-C via a cholera and pertussin toxin insensitive guanine nucleotide binding protein. A specific GTP-binding protein, transducin, has been demonstrated to function in the receptor-mediated activation of phospholipase A_2 and C in bovine retina. Both phospholipases appear to be under inhibitory control in this tissue. Kinases apppear to play a role in the signal transduction of phospholipase A_2 and phospholipase C by modification of the G proteins that couple receptor activation to changes in effector systems within the cell.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00429-09 LCB

PERIOD COVERED

October 1, 1987 through September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biochemistry of Membranes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Zatz	Section Chief	SBP, LCB, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Cell Biology

SECTION

Section on Biochemical Pharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0	0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

1) Previous work explored the mechanisms by which lithium causes ACTH secretion from anterior pituitary cells. It is hypothesized that this effect is mediated by lithium's action on Na^+/Ca^{++} exchange mechanisms. Further work on this problem was postponed.

2) Previous work demonstrated the acylation of rhodopsin by long chain fatty acids *in vivo* and *in vitro*. Further work on the role of this new class of post-translational modification in receptor function was postponed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00424-13 LCB

PERIOD COVERED

October 1, 1987 through September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biologically Active Peptides in the Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.s
Michael J. Brownstein, Chief, Laboratory of Cell Biology, NIMH
T. Bonner, Special Expert, Laboratory of Cell Biology, NIMH
C. Gerfen, Sr. Staff Fellow, Laboratory of Cell Biology, NIMH
M. Palkovits, Visiting Scientist, Laboratory of Cell Biology, NIMH
C. Weinberger, Sr. Staff Fellow, Laboratory of Cell Biology, NIMH
W.S. Young, Sr. Staff Fellow, Laboratory of Cell Biology, NIMH
(see attached)

COOPERATING UNITS *(if any)* Good Samaritan Hosp., Portland, Oregon; Duke U. Med. School; MD, NIDDKD, Purdue Univ.; JHU; LNC, NINCDS; Westminster Hosp., London

LAB/BRANCH

Laboratory of Cell Biology

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
10		0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The structures, distributions, and functions of molecules of importance in the nervous system are being studied. Several cDNAs that encode neurotransmitter receptors have been isolated. The distributions of mRNAs to which these DNAs are complementary have been determined by means of in situ hybridization histochemistry (ISHH) as have the distributions of other mRNAs (e.g., thyroid hormone receptor, G-proteins, phospholipases). ISHH has also been used to examine the effects of physiological and pharmacological manipulations on specific mRNA levels in the CNS. Expression of receptor cDNAs has allowed functional studies to be carried out--especially studies of receptor coupling to second messenger systems.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02296-04 LCM

PERIOD COVERED
October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
In Vivo Tomographic Imaging of Dopaminergic Systems and Their Turnover

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. C. Chiueh	Pharmacologist	LCM, NIMH
Others:	R. M. Cohen	Section Chief	LCM, NIMH
	J.-J. Chen	Visiting Fellow	LCM, NIMH
	D. Doudet	Visiting Associate	LCM, NIMH
	M. Miyake	Visiting Fellow	LCM, NIMH

COOPERATING UNITS *(if any)*
Nuclear Medicine, CC NIH (R. Finn; M. Green); Laboratory of Chemistry, NIDDK (K. Kirk); University of Pennsylvania (H. Kung)

LAB/BRANCH
Laboratory of Cerebral Metabolism

SECTION
Section on Clinical Brain Imaging

INSTITUTE AND LOCATION
National Institute of Mental Health
9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.5	0.5

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The preclinical evaluation of the PET/[F-18]-L-6-F-dopa imaging procedures of brain dopaminergic neurons, including a cyclotron production of radioactive nuclide, radiochemical synthesis and purification of [F-18]-L-6-F-dopa, quality control of radiopharmacy, PET tomographic imaging, and the plasma metabolic profile of the imaging ligand, has been completed by the present study. This PET/[F-18]-L-6-F-dopa brain imaging procedure is ready for clinical study of striatal dopamine neurons. The results of the independent quality control of [F-18]-L-6-F-dopa indicated that the NIH cyclotron and radiopharmaceutical colleagues synthesized routinely this PET imaging ligand with the chemical purity and the specific activity of 97% and 350 mCi/mmol, respectively. This highly purified [F-18]-L-6-F-dopa preferentially imaged dopamine neurons in the brain in vivo with a signal to noise ratio of about 3. In the plasma, 6-F-dopa was decarboxylated and conjugated to form 6-F-dopamine and 6-F-3-methoxy. The major plasma metabolite was identified as O-methylated 6-F-dopa in the monkeys which might interfere the use of 6-F-dopa for brain dopamine turnover study. In collaboration with Dr. Hank Kung of the University of Pennsylvania, we have also developed a new SPECT imaging ligand, [I-123]-labeled IBZM, for studying D2 dopamine receptors. In addition, we have synthesized and purified F-18 labeled uptake blocker, benztropine, and an anti-nerve gas agent, DPET. These newly designed radioligands can be used for imaging muscarinic receptors. Thus, the results of this pre-clinical study have provided potential clinical brain imaging ligands for studying pre- and post-synaptic dopaminergic activities in patients with neuropsychiatric or neurological disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 00507-07 LCM

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical Brain Imaging

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R. M. Cohen	Section Chief	LCM, NIMH
Others:	T. Nordahl	Senior Staff Fellow	LCM, NIMH
	A. Zametkin	Senior Staff Psychiatrist	LCM, NIMH
	W. Semple	Statistician	LCM, NIMH
	D. Doudet	Visiting Associate	LCM, NIMH
	N. Ostrowski	Senior Staff Fellow	LCM, NIMH
	P. Andreason	Senior Staff Fellow	LCM, NIMH

COOPERATING UNITS *(if any)* Clinical Neuroscience Branch, NIMH (Elizabeth Matthew); Clinical Center, Department of Nuclear Medicine, NIH (Richard E. Carson); Neuropharmacology, NIMH (Chawki Benkelfat); Biological Psychiatry Branch, NIMH (Robert M. Post); Child Psychiatry Branch, NIMH (Judith M. Rumsey).

LAB/BRANCH
Laboratory of Cerebral Metabolism

SECTION
Section on Clinical Brain Imaging

INSTITUTE AND LOCATION National Institute of Mental Health
9000 Rockville Pike, Bethesda, MD 20892-1000

TOTAL MAN-YEARS: 8.5	PROFESSIONAL: 4.5	OTHER: 4.0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The major areas of effort in this project have been (1) to develop new approaches to the study of normal and abnormal physiology by positron emission tomography (PET); and (2) to apply available PET tracer methodologies to the study of neuropsychiatric disorders. To these ends the following achievements are notable.

We have begun our first PET studies using [150]-labeled water for the measurement of cerebral regional blood flow. These studies are examining (1) the usefulness of this method for determining regional brain involvement in cognitive processes, (2) the measurement of regional brain response to benzodiazepines and (3) the effect of MPTP lesions on cerebral blood flow.

PET scans of regional glucose metabolism have now revealed a similar prefrontal cortex abnormality in both patients with severe manic-depressive illness and schizophrenia. The abnormally low metabolic rates do not appear to be related to patient symptomatology at the time of scan nor to medication status. The area of the abnormality corresponds to that area of the frontal cortex which the ability to sustain attention is localized to in normals. It is possible that the mid-prefrontal cortex abnormality could represent a vulnerability factor for the development of psychosis. In our first completed study using the new Scanditronix PET scanner, we have observed an abnormally high glucose metabolic rate in the orbital region of patients with obsessive compulsive disorder.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02431-02 LCM

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Intracellular Mechanisms of Carbohydrate Transport and Metabolism in Neurons & Glia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. Nelson	Medical Officer (Research)	LCM, NIMH
Others:	Sokoloff	Chief	LCM, NIMH
	N. Eng	Chemist	LCM, NIMH
	J. Kline	Biol. Lab. Tech.	LCM, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.00	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This report describes studies which are continuing on a project initiated last year in which the cellular and intracellular mechanisms of carbohydrate metabolism and transport are being examined. Experiments which measure glucose-6-Pase (G-6-Pase) activity toward deoxyglucose-6-phosphate (DG-6-P) and mannose-6-phosphate (M-6-P) in rat brain and liver microsomes are still in progress. Liver microsomes have been prepared in optimal state of "intactness" for G-6-Pase measurements (i.e., in the absence of detergent less than 2% of the mannose-6-Pase activity is present which can be found in the presence of detergent). Brain microsomes have been harder to prepare. Microsomal preparations from brain have typically been less than 60% intact as defined by M-6-P hydrolysis. Other investigators have reported the same finding for brain microsomes. Work is continuing with brain microsomes to see if there is a way in which they can be prepared in the essentially intact state. The microsomal preparations will be used to determine the mechanisms of transport of glucose and/or deoxyglucose from the cisterns of the endoplasmic reticulum following hydrolysis of G-6-P or DG-6-P.

A new part of the investigation involves the use of brain microdialysis techniques which are being developed to enable us to determine the intracellular concentration of unmetabolized deoxyglucose and glucose in various normal and abnormal physiological states.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02414-02 LCM

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Metabolic Interdependence of Neurons and Glia

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	E. C. Kaufman	Research Chemist	LCM, NIMH
Others:	B. F. Driscoll	Research Biologist	LCM, NIMH

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	0.85	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

In the continuation of our work on the interrelationship of neurons and glia, we have focussed on the regulation of CO_2 fixation (CO_2 + pyruvate → oxalactate) in glial cells. We have found that this anaplerotic reaction which is located primarily in glial cells is markedly stimulated by increases in extracellular potassium, increases such as those produced by normal neuronal activity or by abnormal activity such as that produced by anoxia or spreading depression. The consequences of changes in CO_2 fixation for both the glial cells as well as the surrounding extracellular fluid has been investigated. The effect of other depolarizing agents has also been studied.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02308-04 LCM

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Growth and Development of Dopaminergic Neurons

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: B. F. Driscoll	Research Biologist	LCM, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Laboratory of Cerebral Metabolism

SECTION
Section on Developmental Neurochemistry

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Survival and development of dopaminergic neurons from embryonic rat mesencephalon were examined in dissociated cell cultures. Survival and the degree of development were assessed by measuring the amount of labelled dopamine taken up by the high affinity dopamine reuptake system. The development of this system correlates well with the development of the dopaminergic neurons.

The dopaminergic neurons develop extensive processes over a period of several weeks in serum free medium. Removal of supernatant from these cultures and replacement with fresh medium leads to delayed damage to the dopaminergic neurons as assessed by a large drop in the activity of the dopamine reuptake system. This damage is also seen morphologically since most of the processes in the culture have an abnormal appearance and many disappear altogether. The damage can be blocked by antagonists of the NMDA class of glutamatergic receptors. However, no exogenous glutamate is added to the culture when the medium is changed and no excess glutamate is detected in the medium surrounding the cells after the medium is changed. Therefore, the identity of the ligand interacting with the NMDA receptor remains to be determined. The sensitivity of the neurons to damage can be modulated by changing the *in vitro* culture conditions indicating that excitotoxic amino acids and their receptors might play an important role in the survival and development of the dopaminergic neurons *in vivo*.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02217-06 LCM

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Plasticity in the Developing Monkey Visual System and the Mouse Somatosensory Sys.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. B. Smith	Research Chemist	LCM, NIMH
Others:	L. Sokoloff	Chief	LCM, NIMH
	P. Melzer	Visiting Fellow	LCM, NIMH
	K. D. Pettigrew	Res. Math. Statistician	TSMB, NIMH

COOPERATING UNITS *(if any)*

Dept. of Otolaryngology, Johns Hopkins Medical School, Baltimore, MD (S. Herdman);
Dept. of Neurology, Johns Hopkins Medical School, Baltimore, MD (R. Tusa)

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.75	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to study the biochemical events associated with plasticity in the nervous system. Protein synthesis is a biochemical process which is involved in bringing about changes in morphology, adjustments in growth rates, and remodeling and maintenance of structure and function. We have, therefore, used the $[^{14}C]$leucine method to study the relationships between local plastic changes which occur and local rates of protein synthesis (LRPS). We are studying two model systems: (a) the developing monkey visual system, and (b) the adult mouse somatosensory system.

A. The developing visual system in the monkey. The postnatal development of the central visual pathways depends on the quality of the visual environment. During the critical period in the primate visual system, environmental manipulation can modify the physiological properties of visual cortical cells.

B. The adult mouse somatosensory system. The whiskers on the muzzle of the mouse have a clear anatomical representation in the somatosensory cortex such that there is a single cortical barrel in layer 4 that corresponds to each whisker. Plasticity in this system during the development of the pathway has been well characterized. Furthermore, there is some electrophysiological evidence that this system retains the ability to reorganize in adult life. We have, therefore, chosen this system to study and characterize as a model for plasticity in the adult.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02216-06 LCM

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Metabolic Mapping of the Brain During Rewarding Self-Stimulation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. J. Porrino	Guest Researcher	LCM, NIMH
Others:	L. Sokoloff	Chief	LCM, NIMH
	S. Young	Guest Researcher	LCM, NIMH
	F. Pontieri	Visiting Fellow	LCM, NIMH
	A. (Tannenbaum) Crane	Research Biologist	LCM, NIMH

COOPERATING UNITS *(if any)* Department of Pharmacology and Psychiatry, Boston University School of Medicine, Boston, MA (C. Kornetsky); Department of Pharmacology, University of Chicago, Chicago, IL (Drs. L. Seiden and M. Kleven); and National Institute of Dental Research, NIH (M. Iadarola)

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.60	1.60	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The deoxyglucose method is being used to study alterations in local cerebral glucose utilization resulting from rewarding electrical brain self-stimulation to discrete brain sites as well as resulting from the administration of drugs of abuse. By mapping metabolic activity in rats under these conditions, information can be obtained about those areas of the brain involved in motivation and reinforcement. Furthermore, the long term neurotoxic effects of drug use and abuse can be assessed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00903-12 LCM

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Purification of Brain Proteinases and Identification of Their Cleavage Products

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	G. E. Deibler	Research Chemist	LCM, NIMH
Others:	T. Burlin	Biologist	LCM, NIMH

COOPERATING UNITS (if any)

Multiple Sclerosis Research Center, Georgetown Univ. Med. Center, Washington, D.C. (J.R. Richert); Lab. of Cereb. Metab., State Univ. of NY Health Sci. Center of Brooklyn, NY (D. Dow-Edwards)

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.2	1.0	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

We are developing procedures to isolate and purify calcium activated neutral proteinases (CANPs) from brain. The bond specificity and cleavage products of these enzymes will be determined.

The valuable collection of myelin basic proteins (MBPs) and peptides derived from them are being used by Dr. John Richert for the identification of different T-cell reactive sites of other MBP-reactive T-cell clones from normal and multiple sclerosis patients. Further investigation of the proliferative response of the forty MBP-reactive T-cell clones from one multiple sclerosis patient revealed two dominant sites of reactivity in MBP. These sites were confirmed with two synthetic peptides (residues 86-105, and 152-170). Synthetic peptide 152-170 also caused a cytotoxic T lymphocyte response in 19 clones.

The collaboration with Dr. Diana Dow-Edwards on the effect of aspartame on the developing guinea pig fetus has resulted in a correlation with the increase of plasma phenylalanine and functional brain development. The increase of tyrosine and tryptophan are also being investigated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE NOTICE OF INTRAMURAL RESEARCH PROJECT	PROJECT NUMBER Z01 MH 00889-10 LCM

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
A Method for the Determination of Local Rates of Protein Synthesis in Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. B. Smith	Research Chemist	LCM, NIMH
Others:	L. Sokoloff	Chief	LCM, NIMH
	C. Kennedy	Guest Researcher	LCM, NIMH
	I. Henrion	Guest Researcher	LCM, NIMH
	G. Deibler	Research Chemist	LCM, NIMH
	K. Schmidt	Computer Systems Analyst	LCM, NIMH
	H. Nakanishi	Visiting Fellow	LCM, NIMH
	Y. Sun	Visiting Fellow	LCM, NIMH

COOPERATING UNITS *(if any)* Dept. Obstet. & Gynecol., U. Fla. (R. Abrams); Dept. Neurosurgery, U. Texas (M. Kadekaro); Dept. Neurosurgery, SUNY (D. Dow-Edwards); Dept. Neurol., U. Mass. Med. Sch. (W.J. Schwartz, T. Scammell); Dept. Anatomy, CUNY Med. Sch. (A. Yu); Dept. Psychiatry, UCSD (J.C. Gillin)

LAB/BRANCH
Laboratory of Cerebral Metabolism

SECTION
Section on Developmental Neurochemistry

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.4	2.1	1.3

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A quantitative autoradiographic method for the determination of local rates of protein synthesis in brain *in vivo* has been developed. L-[1-^{14}C]Leucine is used as the tracer for incorporation of leucine into protein. A four-compartment model for the behavior of leucine in brain has been analyzed, and an equation has been derived that defines the rates of amino acid incorporation into protein in terms of the time course of plasma leucine specific activity, final tissue concentrations of ^{14}C, and λ_{tRNA}, the ratio of the distribution volumes for the labeled and unlabeled leucyl-tRNA pool. The value of λ_{tRNA} for the brain as a whole has been experimentally determined to be 0.58. In the same experiments, the value of $\lambda_{free\ leucine}$, the ratio of distribution volumes for labeled and unlabeled free leucine in brain, was 0.59. Preliminary experiments show that $\lambda_{free\ leucine}$ varies regionally with values ranging from 0.4 to 1.0.

Several studies have been carried out to ascertain the potential usefulness of the method and to examine some basic neurobiological questions. These studies include: 1) normal development; 2) slow wave sleep; 3) barbiturate anesthesia; 4) ketamine anesthesia; 5) electrical stimulation of sciatic nerve; 6) hypothyroidism; 7) circadian rhythms; and 8) effects of testosterone on regenerating neurones.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00887-12 LCM

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Extended Visual System of the Macaque Monkey

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. Kennedy	Guest Researcher	LCM, NIMH
Others:	L. Sokoloff	Chief	LCM, NIMH
	M. Mishkin	Chief	LN, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Neuropsychology, NIMH (M. Mishkin)

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has merged to become one aspect of project Z01 MH 00882-22 LCM.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00882-22 LCM

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies on Regional Cerebral Circulation and Metabolism

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Sokoloff	Chief	LCM, NIMH
Others:	C. Kennedy	Guest Researcher	LCM, NIMH
	T. Nelson	Medical Officer (Research)	LCM, NIMH
	C. B. Smith	Research Chemist	LCM, NIMH
	G. A. Dienel	Senior Staff Fellow	LCM, NIMH
	N. Cruz	Biologist	LCM, NIMH
	K. Schmidt	Computer Systems Analyst	LCM, NIMH

COOPERATING UNITS *(if any)*

Theoretical Statistics & Mathematics Branch, NIMH (C.S. Patlak & K.D. Pettigrew); NINDS, NIH (I. Kopin & L. Porrino)

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
6.5	4.0	2.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The deoxyglucose method for the quantitative determination of rates of local glucose consumption in the discrete functional and structural components of the brain of conscious or anesthetized laboratory animals was developed in this laboratory over 10 years ago. In this method [^{14}C]deoxyglucose is employed as a tracer for glucose flux through the hexokinase step; the product, [^{14}C]deoxyglucose-6-phosphate, is measured by quantitative autoradiography. The method continues to be used to study alterations in local energy metabolism in a variety of physiological, pharmacological and a limited number of pathological states. Its suitability to a wider range of pathologic conditions is being extended and special time constraints which may be present in the method's adaptation for use in human subjects with [^{18}C]fluorodeoxyglucose and PET have been examined.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02307-04 LCM

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Role of Proteinases in Production and Control of Neuropeptides

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. W. Kies	Chemist	LCM, NIMH
Others:	G. E. Deibler	Research Chemist	LCM, NIMH

COOPERATING UNITS *(if any)*

Department of Pathology, University of Washington, Seattle (E.C. Alvord, Jr.)

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS: PROFESSIONAL: OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Due to the death of Dr. Marian W. Kies in December, 1988, this project has merged with Project No. Z01 MH 00903-12 LCM.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02220-06 LCM

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regional Biochemical Changes in the Normal Aging Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. B. Smith	Research Chemist	LCM, NIMH
Others:	L. Sokoloff	Chief	LCM, NIMH
	Y. Sun	Visiting Fellow	LCM, NIMH

COOPERATING UNITS *(if any)*

Department of Biochemistry, University of Tennessee, Knoxville, Tennessee (Dr. J. Joshi)

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effects of normal aging in rats on cerebral metabolic processes have been studied. With the application of local methods developed in this Laboratory, rates of two processes can be determined in discrete regions of the brain in normal conscious animals: (A) glucose utilization and (B) protein synthesis.

A. Glucose Utilization. In aged rats, rates of glucose utilization are decreased in the components of the primary auditory and visual pathways. In addition, glucose utilization in the striatum is particularly and significantly decreased. In order to examine the functional consequences of these senescent changes in the nigrostriatal dopaminergic system, we are studying the effects of aging on the metabolic responsiveness to the dopaminergic agonist, apomorphine. These studies are in progress.

B. Protein Synthesis. Rates of protein synthesis are also decreased in aged rats in components of the primary auditory and visual pathways. The changes may be the consequences of a chronic lack of sensory input due to age-related degenerative changes in both retina and inner ear.

Aluminum toxicity has been proposed as an etiological factor in Alzheimer's Disease and aluminum has been shown to affect numerous biochemical processes including several enzymes in the metabolic pathway for glucose. Experiments are in progress on the effects of prolonged (2 years) intake of low levels of aluminum in drinking water on local cerebral glucose utilization in aged rats.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00881-33 LCM

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Intermediary Energy Metabolism in Mammalian Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E. E. Kaufman	Research Chemist	LCM, NIMH
Others:	T. Nelson	Medical Officer (Research)	LCM, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Chemistry, NHLBI (Henry M. Fales)

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.60	0.35	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This report will describe our most recent findings on the new mammalian transhydrogenase. This enzyme catalyzes the transfer of hydrogen from specific hydroxyacids to equally specific oxoacids. Progress has been made in the purification of the enzyme as well as identifying naturally occurring hydroxyacids and oxoacids which function either as substrates or as inhibitors of the enzyme.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02462-01 LGCB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

S-Adenosylmethionine and Affective Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	G.L. Cantoni	Chief, Laboratory of General and Comparative Biochemistry	LGCB	NIMH
	S.H. Mudd	Guest Researcher	LGCB	NIMH
	V. Andreoli	Guest Researcher		

COOPERATING UNITS *(if any)*

Department of Psychiatry, St. John Hospital (Soave-Verona), and University of Verona, Italy

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Proteins

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	1	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

S-Adenosyl-L-methionine (AdoMet) is a safe and probably effective antidepressant agent in certain forms of clinical depression. A new hypothesis is offered to account for the mechanism of action of S-adenosylmethionine in such illness, based upon the known biochemistry of this compound, and upon current knowledge of clinical and genetic aspects of affective disorders. We postulate that at least some major mood disorders are due to abnormalities affecting the AdoMet-dependent methylation of a substance in the central nervous system. For convenience and without prejudging the chemical structure of this substance, we term it for the moment "barinine." The model requires that barinine be subject to AdoMet-dependent methylation and that methylbarinine be subject to metabolic demethylation to regenerate the original barinine. Methylbarinine should be mood elevating, whereas barinine itself should not be. Depression is a result of abnormalities lowering the normal steady-state concentration of methylbarinine, while mania results from an abnormal elevation of methylbarinine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER
Z01 MH 02321-04 LGCB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
DNA Methylation and Gene Expression

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	G.L. Cantoni	Chief, Laboratory of General and Comparative Biochemistry	LGCB NIMH
	A. Razin	Visiting Scientist, The Hebrew University, Jerusalem, Israel	
	F. Gros	Visiting Scientist, Pasteur Institute, Paris, France	

COOPERATING UNITS *(if any)*
Department of Cellular Biochemistry, The Hebrew University, Hadassah Medical School, Jerusalem, Israel; Department of Molecular Biology, Pasteur Institute, Paris, France

LAB/BRANCH
Laboratory of General and Comparative Biochemistry

SECTION
Section on Proteins

INSTITUTE AND LOCATION
NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Transient DNA hypomethylation is observed when murine erythroleukemia cells (MELC) are induced to differentiate. The fact that this phenomenon takes place in the absence of DNA replication led us to the discovery of a novel reaction whereby a modification in the pattern of DNA methylation is brought about by the specific removal of methyl cytidine (mC) residues and their replacements by cytidine. The transient nature of DNA hypomethylation indicates that this event must be followed by de novo DNA methylation, and indeed we have previously shown that such is the case. Treatment of MEL cells with 3-DZA (3-deaza-Ado) and homocysteine will completely inhibit the expression of the differentiated state (measured at 72-96 hours) if these agents are added between 8 and 20 hours after induction; if 3-DZA + Hcy are added together with the inducer but removed 8 hrs later there is no effect on differentiation. If administration of DZA + Hcy is delayed for 24 hrs after induction differentiation proceeds normally. We have established furthermore that the reaction catalyzed by 5-mC replacase is inhibited in parallel fashion and with the same time frame. Thus during the process of differentiation, but long before its expression, there is "window" when one or more biochemical reactions are susceptible to inhibition by DZAHcy. Since we have recently observed that HMBA induced hypomethylation is not affected by inhibition of protein synthesis we have reached the tentative conclusion that 5-mC replacase is present in an inactive form in exponentially growing MEL cells and becomes active upon induction through carboxymethylation. The striking correspondence in the timing of the inhibition of differentiation and of the HMBA induced DNA hypomethylation produced by 3-DZA + Hcy adds weight to the hypothesis that this limited and specific modification of DNA structure is one in a series of events that are required for the expression of the differentiated genotype.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00931-16 LGCB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders.)*

Characteristics and Regulation of S-Adenosylhomocysteins Hydrolase

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	P.S. Backlund, Jr.	Research Chemist	LGCB NIMH
	R.R. Aksamit	Research Chemist	LGCB NIMH
	G.L. Cantoni	Chief, Laboratory of General and Comparative Biochemistry	LGCB NIMH

COOPERATING UNITS *(if any)*

Department of Biochemistry, Toyama Medical and Pharmaceutical University, Toyama, Japan

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Proteins

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4	2.5	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

S-Adenosylhomocysteine hydrolase plays a critical role in regulating AdoMet-dependent methylations in eukaryotic cells by regulating the ratio of AdoMet/AdoHcy. It is the only enzyme in eukaryotic cells for the removal of AdoHcy, the end-product of biological transmethylation reactions. Several approaches are being used to determine the structure and function of this enzyme.

1) Structure Determination: We have cloned the cDNA for the enzyme from both rat liver and D. discoideum cDNA libraries. The amino acid sequence was determined and a putative NAD binding site identified. Comparison of the amino acid sequence of the rat liver with the Dictyostelium enzyme indicates that 74% of the amino acids are identical, suggesting that much of the sequence is required for enzyme function. Expression of the cloned cDNA of the rat liver enzyme in E. coli and site-directed mutagenesis have allowed us to determine the function of specific amino acid residues in NAD binding and catalytic activity of the enzyme.

2) Genomic Organization and Expression: AdoHcy hydrolase is expressed at a very high level in liver, and is also present at lower levels in all tissues examined. The expression of the AdoHcy hydrolase mRNA in different tissues and the genomic organization of the AdoHcy hydrolase gene in rat are under investigation.

3) Biological Effects: Because of the pivotal role of S-adenosyl homocysteine hydrolase in biological methylations, the enzyme is an important potential target for inhibitors that may have a variety of useful pharmacological effects. A large number of adenosine and adenosylhomocysteine analogs have been examined for their ability to function as inhibitors and/or substrates of S-adenosylhomocysteine hydrolase. In vivo these adenosine analogs have a wide range of biological activities, including antiviral activity against several RNA and DNA viruses, inhibition of leukocyte chemotaxis, and modulation of cell differentiation

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02228-05 LMB

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Genetic Neurobiology of Drosophila

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. A. Nash	Chief, Sec. on Molecular Genetics	LMB, NIMH
Others:	K. S. Krishnan	Visiting Scientist	LMB, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Molecular Biology

SECTION
Section on Molecular Genetics

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.32	1.16	0.16

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project exploits genetic manipulation in the fruit fly, Drosophila melanogaster, to discover and analyze components of the nervous system concerned with the phenomenon of general anesthesia. In the past we have successfully isolated mutants of Drosophila that are relatively resistant to the anesthetic effects of halothane, a clinically useful general anesthetic. We have now developed a simple "separator" assay that can be performed repeatedly on small numbers of flies. When this feature is coupled with improved care in the handling of flies that are to be used in the test, reliable data result. We have successfully carried out four kinds of genetic characterization on a set of three mutant strains. Our preliminary data have roughly mapped one dominant allele and indicate that both recessive alleles are uncovered by a short deletion of the chromosome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 01037-21 LMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Role of the Cell Membrane in Cellular Organization: A Molecular Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. M. Neville, Jr.	Chief, Sec. on Biophys. Chem.	LMB, NIMH
Others:	T. H. Hudson	Staff Fellow	LMB, NIMH
	J. W. Marsh	Staff Fellow	LMB, NIMH
	K. Srinivasachar	Visiting Associate	LMB, NIMH
	H. Wellhöner	Guest Researcher	LMB, NIMH

COOPERATING UNITS *(if any)*

Department of Toxicology, Medical School of Hannover, FRG

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Biophysical Chemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS: 6	PROFESSIONAL: 4	OTHER: 2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The general aim of this project is to elucidate mechanisms by which proteins and viruses enter cells by receptor-mediated transport processes and translocate across the lipid bilayer to the cytosol and nuclear compartments. Molecular signals which lead to unique vesicle trafficking are studied. A major new tool is the use of low light level fluorescence digital imaging. Assays are developed which quantitatively define the efficiency of membrane translocation. Macromolecular chemical determinants which affect translocation, and cellular energy sources which drive translocation are determined. Utilizing basic data from such studies, immunotoxins (toxins linked to monoclonal antibodies) are constructed to serve as a new class of pharmacologic reagents to eliminate unwanted cell types such as cancer cells or T-4 lymphocytes and macrophages in AIDS infections, or to manipulate specific cells such as T cell and B cell subsets to correct imbalances which exist in autoimmune diseases that affect the CNS, such as multiple sclerosis and lupus and cause psychosis. In addition, immunotoxins continue to prove useful in diminishing the incidence of graft-versus-host-disease following bone marrow transplantation and thus will also have utility in enzyme replacement therapy and organ transplantation. The relationship between the uptake of exogenous proteins and viruses and the processing of these materials for immunological recognition in association with Class I and Class II MHC molecules is also studied. A clinical application of this program is the development of cells with anti-viral anti-sense oligonucleotides coupled to receptor-mediated protein shuttles via cleavable acid-labile crosslinking reagents.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 01035-21 LMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Process of Lysogeny

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. A. Nash	Chief, Sec. on Molecular Genetics	LMB, NIMH
Others:	M. Bruist	Research Associate	LMB, NIMH
	S. Goodman	Staff Fellow	LMB, NIMH
	A. Granston	IRTA Fellow	LMB, NIMH
	G. Smith	Guest Researcher	LMB, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Mathematical Biology, National Cancer Institute

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.50	3.25	1.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The integration of bacteriophage lambda depends upon two proteins: the virally encoded Int and the host encoded IHF. Both interact specifically with different segments of the viral recombination site, *att*P. We have tested the hypothesis that IHF functions as an architectural element by replacing one of the IHF sites in *att*P by either of two unrelated modules that, like IHF, bend DNA. Our success provides the first demonstration for any bending protein that the change of shape is biologically significant and not just a consequence of the way the protein binds to DNA.

A series of detailed footprinting studies has shown that IHF represents a novel class of specific DNA binding protein. The footprint has several notable features that strongly implicate the minor groove of DNA as the primary contact surface for IHF, an unprecedented mode for a sequence specific binding protein. Using structural parameters of the IHF family, our determination that IHF makes a 1:1 complex with each of its sites, and computer modeling, we have come up with a specific model for how IHF binds to and bends DNA.

We have used an unusual substrate, recombination sites containing mismatches, to help in the analysis of strand exchange during lambda integration. Although the heteroduplex sites are specifically cleaved by Int topoisomerase, rejoining of the broken DNA is hindered and heteroduplexes accumulate broken intermediates which are then processed in novel ways. We have used this feature to make several new findings about the control of directionality of recombination. With these substrates we also found that Int topoisomerase can form recombinants with either of two genetic polarities; this provides the first hint that the mechanism of the well characterized bacterial systems may be related to that seen in immunoglobulin rearrangement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 00934-17 LMB

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Biochemical Basis of Peptide Receptor Activity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. A. Klee	Chief, Sec. on Regulatory Proteins	LMB, NIMH
Others:	D. L. Newton	Staff Fellow	LMB, NIMH
	T. Osugi	Visiting Fellow	LMB, NIMH
	H. Sohma	Visiting Fellow	LMB, NIMH
	R. C. Rice	Chief, Lab. Med. Chem.	LMC, NIDDK
	A. E. Jacobson	Research Chemist	LMC, NIDDK
	H. G. Coon	Cell Biologist	LG, NCI
	P. Hargrave	Professor of Ophthalmology	University of Florida

COOPERATING UNITS *(if any)*

Laboratory of Neurophysiology, NINCDS; Laboratory of Chemistry, NIDDK; Laboratory of Genetics, NCI; and Laboratory of Molecular Biology, NIDDK

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Regulatory Proteins

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	4.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

It has become clear that the members of the class of cell surface receptors coupled to G-proteins each can exhibit several different actions including: activation or inhibition of adenylate cyclase, activation of phospholipases, activation of phosphodiesterase, or effects upon ion channels. Each of these activities results from the prior activation of one or more G-proteins by the receptor. Understanding many aspects of receptor activity at the biochemical level is thus reduced to the problem of clarifying receptor-G-protein interactions. By the combined use of specific antibodies and synthetic peptides we have characterized a receptor domain that activates G-proteins. Studies of G-protein reconstitution with adenylate cyclase in lipid vesicles have provided evidence for the direct interaction of one of several such G-proteins with the enzyme, thus providing an alternate mechanism for inhibition of the enzyme by hormones. In related studies, we have also developed a general method to inactivate G-proteins in membranes so as to then be able to reconstitute receptor function by adding the appropriate, unmodified, G-protein. A new project, initiated in the past year, involves studies of the solubility properties of different conformational states of the alpha subunits of some G-proteins coupled with a serious attempt to prepare single crystals of such proteins suitable for X-ray crystallography. In related work, we have initiated studies aimed at improving the methods for predicting protein structures based upon amino acid sequence information.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01040-21 LNC

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Molecular Biology of the Pterin-Dependent Hydroxylases and Ancillary Enzymes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Seymour Kaufman	Chief	
	Sheldon Milstien	Research Chemist	LNC NIMH
	Bruce Citron	Senior Staff Fellow	LNC NIMH
	Jennifer Tipper	Senior Staff Fellow	LNC NIMH
	Michele Belecanech	Biologist	LNC NIMH
	Brenda Yanak	Visiting Student	LNC NIMH
	Wendy Chung	Summer Biologist	LNC NIMH

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN YEARS	PROFESSIONAL:	OTHER
2.14	2.6	0.8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

A full length rat phenylalanine hydroxylase cDNA has been constructed and expressed in *E. coli* to produce large amounts of active enzyme. Kinetic parameters have been measured to compared this enzyme to a construct with an altered putative regulatory domain and other specific mutant enzymes which are under construction.

Preliminary data concerning the hormonal regulation of phenylalanine hydroxylase in diabetic rats indicates that loss of insulin leads to increased enzyme and message levels.

The human phenylalanine hydroxylase coding sequence has been cloned and characterized by sequencing. The initial steps to express this enzyme in *E. coli* have been completed.

Human dihydropteridine reductase cDNA has been subcloned to a more efficient expression vector and maximal levels of enzyme have been synthesized *in vitro*.

Rat sepiapterin reductase has been isolated by antibody screening and confirmed by sequencing DNA and tryptic peptides. This is the first known clone of an enzyme in the biosynthetic pathway for the cofactor tetrahydrobiopterin. Aromatic amino acid hydroxylation, and hence dopaminergic and serotonergic neurotransmitter synthesis, is dependent on this cofactor.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01039-21LNC

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pteridine Biosynthesis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Sheldon Milstien	Research Chemist	LNC NIMH
	Seymour Kaufman	Chief	LNC NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.7	0.7	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The terminal enzyme in the pathway for tetrahydrobiopterin (BH_4) biosynthesis, sepiapterin reductase, has been partially sequenced and a full length cDNA clone isolated. Studies are now underway to isolate cDNAs for the other enzymes on pathway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01038-21LNC

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Phenylketonuria and Other Diseases Caused by Defects in Biopterin-Dependent Enzymes

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	Seymour Kaufman	Chief	LNC NIMH
	Sheldon Milstien	Research Chemist	LNC NIMH
	Keiko Tanaka	Guest Worker	LNC NIMH

COOPERATING UNITS (if any)

Stanley Rapoport, Chief LN NIA

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.20	2.20	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Patients with Retts syndrome have lower than normal CSF levels of metabolites of monoamine neurotransmitters and abnormally high CSF levels of tetrahydrobiopterin.

CSF levels of BH_4, HVA and 5HIAA are lower than normal in two subtypes of patients with Alzheimers disease, those with extrapyramidal symptoms and those with myoclonus.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE **NOTICE OF INTRAMURAL RESEARCH PROJECT**	PROJECT NUMBER Z01 MH 01031-21LNC

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Conversion of Phenylalanine to Tyrosine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Seymour Kaufman	Chief	LNC NIMH
	Michael Davis	Senior Staff Fellow	LNC NIMH
	Masao Hirose	Visiting Associate	LNC NIMH
	John Giovanelli	Research Chemist	LNC NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.10	3.10	2.00

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The normal intermediate in the hydroxylation reaction, the 4-α-hydroxytetrahydropterin, is formed when phenylalanine hydroxylase catalyzes the completely uncoupled reaction.

The reason why phenylalanine hydroxylase in hepatoma cells is more active than the normal liver enzyme is that the hepatoma enzyme is more highly phosphorylated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01032-21LNC

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biosynthesis of Catecholamines

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Seymour Kaufman	Chief [illegible]	LNC NIMH
	Paula Ribeiro	Visiting Fellow	LNC NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.20	1.20	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Tyrosine hydroxylase (TH) was purified and partially characterized from the rat pheochromocytoma cell line PC 18. The kinetic properties and substrate specificity of the tumor enzyme resembled those of TH from striatum and adrenal medulla. In addition, the pure TH from PC 18 cells could be phosphorylated using cAMP-dependent protein kinase. The amount of phosphate incorporated into the enzyme and the resulting increase in activity also correlated well with TH from other sources. Finally, evidence was provided for the existence of a phosphatase in striatum and PC 18 cells which mediated the dephosphorylation of tumor TH. The properties and regulation of this phosphatase are currently under investigation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01100-01 LNP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of the Somatic Sensorimotor System in Rodents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Timothy M. Barth	Staff Fellow	LNP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH Animal Center, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☑ (c) Neither

  ☐ (a1) Minors

  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to examine the mechanisms of recovery of function following damage to the neocortex in adult and neonatal rats. We have focussed on several subregions of the somatic sensorimotor cortex and have used a battery of tasks sensitive to impairments in tactually-guided behavior. This project includes a detailed examination of the somatosensorimotor impairments following small cortical lesions, a comparison between the recovery patterns of rats receiving lesions as adult vs neonates and the effects of MK-801 (an noncompetitive antagonist at the N-methyl-D-aspartate receptor) on the rate of recovery in adult rats. The rat is the model species because the sensorimotor effects of lesions have been studied most extensively in this species.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01098-03 LNP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Anatomical Analysis of Neuronal Circuits

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Chisato Asanuma Stanfield	Senior Staff Fellow	LNP, NIMH
Others:	Linda L. Porter	Asst. Prof., Dept. Anat.,	USUHS

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH Animal Center, Poolesville, Maryland 20837

TOTAL MAN-YEARS: 1.1	PROFESSIONAL: 1.1	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A dense axonal projection arising in the caudal magnocellular basal nucleus (cMBN) and terminating within the thalamic reticular nucleus (TRN) was identified in rats. By combining the axonal transport and the subsequent immunohistochemical localization of PHA-L with intracellular injections of the fluorescent dye, Lucifer yellow into identified TRN neurons, axons of the cMBN ⇒ TRN pathway were found to give rise to clusters of boutons apposing TRN neuronal somata as well as 'en-passant' beads apposing TRN neuronal dendrites.

The terminal boutons of the cMBN ⇒ TRN pathway were examined at the electron microscope (EM) level following PHA-L injections into the cMBN. Following the immunohistochemical processing, many PHA-L positive terminal profiles forming synaptic contacts upon TRN neurons are apparent. Labeled axonal terminals frequently synapse upon both somata and proximal dendrites of TRN neurons, with symmetric membrane specializations. These may, therefore, differ from the ChAT positive synapses within the TRN which are asymmetric and terminate upon distal dendritic processes. Other PHA-L labeled axonal terminal profiles synapse upon distal dendrites with asymmetric membrane specializations. These asymmetric synapses may correspond to ChAT positive synapses.

Following WGA-HRP injections into the TRN, neurons were identified within the cMBN that are both retrogradely labeled and positive for GABA. Such double labeled neurons occur in the same general cMBN region as ChAT positive neurons that project to the TRN.

We infer from these that at least a portion of the cMBN ⇒ TRN projection is GABAergic. Since GABA iontophoresis inhibits TRN spike activity by increasing chloride ion permeability, this pathway may, in part, serve to directly 'shunt' the somatic excitability of TRN neurons, and hence indirectly disinhibit the relay nuclei of the thalamus. This adds the prospect of a substantial telencephalic control over the long held 'brainstem' ascending reticular activating concept since the cMBN ⇒ TRN pathway is optimally poised to serve as an integral link in the neuronal mechanisms which serve to precipitate and modulate the flow of information from the periphery to the cerebral cortex during vigilance.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01096-05 LNP

PERIOD COVERED

October 1, 1988 to January 29, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Spatial Organization of the Primate Motor Cortex

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Andrew R. Mitz	Senior Staff Fellow	LNP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH Animal Center, Poolesville, Maryland 20837

TOTAL MAN-YEARS: 0.0	PROFESSIONAL: 0.0	OTHER:

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Dr. Mitz was converted, this fiscal year, from Senior Staff Fellow to Biomedical Engineer, GS-12. As such, project Z01 MH 01096 LNP is suspended and such research as in continuing is re-incorporated into Z01 MH 01092-11 LNP, Dr. Wise, principal investigator.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01092-11 LNP

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Frontal Lobe and the Cerebral Control of Behavior

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Steven P. Wise	Research Biologist	LNP, NIMH
Others:	Andrew R. Mitz	Biomedical Engineer	LNP, NIMH
	Shraga Hocherman	Visiting Associate	LNP, NIMH
	Giuseppe di Pellegrino	Visiting Fellow	LNP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH Animal Center, Poolesville, Maryland 20837

TOTAL MAN-YEARS: 3.7	**PROFESSIONAL:** 3.7	**OTHER:**

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Laboratory of Neurophysiology primarily concentrates on the application of behavioral neurophysiology to the study of frontal lobe function and organization. The primate frontal lobe consists of three main parts: the primary motor cortex (M1), the prefrontal cortex (PF), and the nonprimary motor cortex. The nonprimary motor cortex can be divided into at least two fields: the supplementary motor cortex (M2) and the premotor cortex (PM). Our results support the hypothesis that, among their functions, PM and M2 play a role in the preparation for future action. This year we have made substantial progress in understanding the aspects of motor preparation in which PM functions. Our neurophysiological studies show that PM functions in retrieving, from a memory store, the movement that needs to be made on the basis of stimulus context. Further, we have shown that the cell activity in PM guides more than merely the attainment of the target or goal of the movement; the precise details of the motor trajectory are very important to PM cellular activity. In addition to our behavioral neurophysiological studies, electroanatomical and cytoarchitectonic techniques have enabled an improved identification of individual cortical fields and a better understanding of the overall organization of the frontal lobe in primates.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH02468-01 BCG

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mechanisms of Action of Psychoactive Drugs

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Xiao-Ming Gao	Visiting Fellow	BCG, NIMH
Others:	De-Maw Chuang	Group Chief	BCG, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Biochemical Genetics

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	1.1	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In an effect to elucidate the mechanisms of carbamazepine and lithium in the treatment of manic depressive illness, we have studied effects of long-term exposure of neurons to carbamazepine and lithium on phosphoinositide hydrolysis by phospholipase C using cultured cerebellar granule cells as a model. 3-day exposure of granule cells to therapeutic concentrations of carbamazepine (30-50 µM), resulted in significant decrease in phosphoinositide turnover elicited by the muscarinic cholinergic receptor agonist, carbachol. A rebound increase of carbachol-induced phosphoinositide turnover was noted at day 4-5 and this was followed by another decline of the receptor-mediated response. Phosphoinositide turnover eliminated by 5-HT, norepinephrine and histamine as well as basal activity were much less affected by long-term carbamazepine treatment.

In parallel experiments, we found that 3-day exposure of cultured granule cells to low concentration (10 mM) of lithium enhanced basal and carbachol-induced phosphoinositide turnover, while exposure to high concentration (10-30 mM) of this ion resulted in a sharp decrease of the carbachol response without significantly affecting basal value. This decrease was due to a major reductionin the maximal stimulation by carbachol. Time course studies revealed that exposure of cells to 5mM lithium markedly enhanced carbachol-induced effect up to day 3 and this was followed by a decline below basal value after day 5-7. Our results are consistent with the hypothesis that alteration of receptor-mediated phosphoinositide hydrolysis is the target of carbamazepine and lithium during the course of long-term treatment and could be pertinent to their therapeutic effects.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH02467-01 BCG

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Receptors for Endothelin and Sarafotoxin in Neurons

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Wan-Wan Lin	Guest Researcher	BCG, NIMH
Others:	De-Maw Chuang	Group Chief	BCG, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Biochemical Genetics

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Using primary culture of cerebellar granule cells, we found that both endothelin (ET) and sarafotoxin (ST) at low concentration range (0.1-300nM) caused a robust and concentration-dependent increase of ^{3}H-inositol phosphates. This phosphoinositude (PI) hydrolysis caused by both peptides was dependent on extracellular calcium but was not significantly affected by either organic or inorganic calcium entry blockers. The net increase of ET-induced PI hydrolysis was not significantly altered by the depletion of extracelluair sodium. ET-induced PI breakdown was partially inhibited by a phorbol ester but was unaffected by pertussis toxin. Effects of ET and ST were nonadditive, but appeared to be additive to that induced by carbachol, histamine, NE, serotonin, glutamate and maitotoxin. Pre-exposure of cells to ET or ST for 30 seconds to 6 hours resulted in densensitization to subsequent stimulation with each peptide, without affecting subsequent responsiveness induced by carbachol, histamine, NE, serotonin, glutamate and maitotoxin. Thus, cerebellar granule cells appear to express a common population of receptors for ET and ST, which are coupled to PI hydrolysis by phospholipase C and display homologous desensitization. The experiments of neurotransmitter release indicated that both peptides at 10nM induced an increase in the release of the glutamate analogue [^{3}H]-D-aspartate preloaded to cerebellar granule cells in culture. Therefore, cultured cerebellar granule cells can provide an excellent model for investigating the biochemical mechanisms and physiological role of ET receptors in the brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01MH 02466-01 BCG

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuropathogenesis in AIDS

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Rita Anand, Ph.D.	Special Expert	LBG/NIMH
Other:	Sanjeev Nayyar, M.D.	Visiting Fellow	LBG/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Biochemical Genetics

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, St. Elizabeths Hospital, Washington, DC 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	2	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A. Neurovirology. The pathogenesis of human immunodeficiency virus (HIV)-induced encephaopathy is being studied by using two approaches. Firstly, by understanding the interaction of HIV-1 isolates, in general, with the neural tissues. Secondly, by detailed biological and molecular characterization of HIV-1 variants isolated from persons with neurological deficiencies, especially in the absence of overt immune suppression. The second approach is expected to elucidate if certain strains of HIV-1 are uniquely neuropathic. The virus-cell interaction studies have shown that human neural cell lines can be transfected with HIV DNA resulting in transient virus replication. Currently, our preliminary findings using primary rodent brain cultures reveal that HIV can partially replicate in these cells upon direct infection, and is specifically cytopathic to neural cells. We have biologically and molecularly characterized one of HIV-1 isolates ($HIV\text{-}1_{BR}$) and have observed the presence of a 39-base duplication of nucleotides in the nef gene.

B. Antiviral Agents. We have investigated the anti-HIV activity of sodium pentosan polysulfate (PPS), a sulfated sugar compound, in normal human peripheral mononuclear cells (PMNC). PPS has potent anti-HIV activity, shows profound anti-HIV synergism with AZT, is essentially nontoxic to PMNC and has lymphoproliferative effect in culture.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02378-03 BCG

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.) Histochemical Localization of Phe-Leu-Phe-Gln-Pro-Gln-Arg-Phe-NH_2 Immunoreactivity in Mammalian CNS

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	T. Salminen	Visiting Fellow	BCG, NIMH
Other:	H-Y.T. Yang	Pharmacologist	BCG, NIMH

COOPERATING UNITS (if any)

C.-H. Lee, Naval Medical Research Institution, Bethesda, MD 20892

LAB/BRANCH

Laboratory of Biochemical Genetics

SECTION

Section on Neuropeptides

INSTITUTE AND LOCATION

National Institute of Mental Health, Saint Elizabeths Hospital, Washington, DC 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

This project has been terminated because the principle investigator has left NIMH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02301-04 BCG

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Functional Role of Adrenal NPY

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K. Shimoda	Visiting Scientist	BCG, NIMH
Other:	H.-Y.T. Yang	Section Chief	BCG, NIMH

COOPERATING UNITS *(if any)*

Maciej Poltork, NIMH, Neuroscience Center at Saint Elizabeths Hospital, Washington, DC 20032

LAB/BRANCH

Laboratory of Biochemical Genetics

SECTION

Neuropeptides

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, DC 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Neuropeptide Y (NPY) is present in very high concentrations in many catecholamine-containing chromaffin cells in the adrenal glands of various species. In this study, a primary culture of rat adrenal medullary cells was developed to study the functional role of NPY in catecholamine secretion from the chromaffin cells. The cultured chromaffin cells were found to release both NPY and catecholamine when stimulated with nicotine. The release of catecholamine was augumented if NPY antibody was added to the medium. This and our previous results suggest that, in the adrenal gland, NPY may be co-released with catecholamines and then act as a physiological neuromodulator on catecholamine secretion. Interestingly, the cultured rat adrenal medullary cells were found to survive for a very long term of culture. Furthermore, the two months old cultured cells were found to extend neurites spontaneously if the culture media were not changed for a week. An experiment is in progress to determine whether trophic material is produced and accumulated in the culture medium. Previously, we found that besides NPY there is an additional NPY-like peptide in the adrenal glands of bovine and rat. This NPY-like peptide has now been purified and biochemically characterized to be identical to NPY(1-30); a radioimmunoassay for this peptide has also been established. The tissue distribution of NPY(1-30) in the adrenal gland is under investigation.

The proposed course of this study is to further determine whether trophic material is produced by the primary culture of the rat adrenal medullary cells with the aim of eventually characterizing this trophic substance. The physiological role of NPY(1-30) will also be explored.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02299-04 BCG

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Receptor Mediated Phosphoinositide Turnover

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	De-Maw Chuang	Group Chief	BCG, NIMH
Others:	Ora Dillion-Carter	Chemist	BCG, NIMH

COOPERATING UNITS (if any)

Carmine Cuscia, Ph.D. - Department of Biochemistry, St. Louis University, MO.

LAB/BRANCH

Laboratory of Biochemical Genetics

SECTION

Group on Receptor Pharmacology

INSTITUTE AND LOCATION

National Institute of Mental Health, Saint Elizabeths Hospital, Washington, DC 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

Using neuroblastoma hybrid NCB-20 as a model, we have characterized receptor-mediated phosphoinositide metabolisms and investigated the regulation of these receptor response. NCB-20 cells contain muscarinic cholinergic, histaminergic H_1 and bradykinin receptors coupled to phosphoinositide hydrolysis by phospholipase C. These receptor-mediated events were calcium-dependent, phorbol ester-sensitive and partially inhibited by pertussis toxin. Pre-exposure of cells to either bradykinin or muscarinic receptor agonist, carbachol, resulted in homologous desensitization in phosphoinositide breakdown but heterologous desensitizationin in mobilizing intracellular calcium. Activators of voltage-sensitive sodium channel such as batrachotoxin and a sodium ionophore, monensin also activated phospholipase C activity. These effects were independent of sodium influx, speaking against the involvement of Na^+/Ca^{2+} exchange in this activation. Veratridine was found to modulate carbachol response by drastically increasing its EC_{50} value, presumably due to receptor-effector uncoupling. Adenosine acting through its receptor selectively inhibited the response mediated by histamine H_1 receptor. Molecular mechanisms underlying these receptor cross-talks are under investigation. We also have studied the pathways involved in the induction by sodium butyrate of muscarinic and δ opioid receptors. Our recent results showed that the newly synthesized receptors are transported via light membrane vesicles as receptor-G protein complexes to the plasma membranes for functional expression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH02298-04 BCG

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT (*[illegible] characters or less. Title must fit on one line between the borders.)*

Receptor Regulation in Cultured Cerebellum Granule Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Onn-Foh Yu	Guest Worker	BCG, NIMH
Others:	Ora Dillion-Carter	Chemist	BCG, NIMH
	De-Maw Chuang	Group Chief	BCG, NIMH

COOPERATING UNITS *(if any)*

Dr. Frescia L. Huang, National Institute of Child Health and Human Development

LAB/BRANCH

Laboratory of Biochemical Genetics

SECTION

Group on Receptor Pharmacology

INSTITUTE AND LOCATION

National Institue of Mental Health, St. Elizabeths Hospital, Washington, DC 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	1.4	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Various aspects of receptor regulation have been studied using primary culture of cerebellar granule cells. These cells express muscarinic cholinergic, histaminergic, α_1-adrenergic and 5-HT_2 sertoninergic receptors coupled to phospholipase C. Exposure of cells to each of the receptor agonist led to time-dependent homologous desensitization. Experiments using H_7 to inhibit protein kinase C activity and long-term treatment with phorbol esters to depletion this enzyme suggested that agonist-induced desensitization is not due to feedback regulation by activated protein kinase C. Receptor down-regulation occured only after the onset of desensitization. Long-term treatment of cells with 50 μM γ-aminobutyric acid (GABA) selectively up-regulated the phosphoinositide responses mediated by quisqualate glutamate receptor subtype and muscarinic cholinergic receptor. The up-regulation of quisqualate response was blocked by a $GABA_A$ receptor antagonist, SR95531, while the effect on muscarinic receptor was mimicked by a $GABA_B$ agonist, baclofen. We have also studied the neurotoxic and neurosurviving effects of drugs in granule cell cultures. Nitroprusside, which increases cGMP level, was found to reduce intracellular calcium content and shorten life span of granule cells in culture. We propose that appropriate level of intracellular calcium is crucial to maintain cell survival and that cGMP may display its neurotoxic or neurosurviving effects on neurons by modulating the level of intracellular calcium. In addition, we found that granule cells express type II and type III protein kinase C, which have differential developmental patterns. In response to glutamate stimulation, type II and type III kinases were translocated from cytosol to distinct membranous fractions. This protein kinase C translocation may be involved in the neurotoxicity and neurotrophic effect of glutamate.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01577-06 BCG

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Characterization of Serotonin Pre- and Postsynaptic Components in NCB-20 Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J-M Cossery	Visiting Fellow	BCG, NIMH
Other:	De-Maw Chuang	Group Chief	BCG, NIMH

COOPERATING UNITS *(if any)*

J-M Mienville, Fidia Georgetown Neuroscience Institute

LAB/BRANCH

Laboratory of Biochemical Genetics

SECTION

Group on Receptor Pharmacology

INSTITUTE AND LOCATION

National Institute of Mental Health, Saint Elizabeths Hospital, Washington, DC 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

NCB-20 is a clonal cell line of neuroblastoma x fetal hamster brain cell hybrid. We have previously shown that these cells express serotonin presynaptic components including a 5-HT uptake system and specific binding sites for the antidepressant imipramine. In the present study, we characterized biochemically and pharmacologically 5-HT-sensitive adenylate cyclase. We also demonstrated a 5-HT$_3$ receptor-mediated inward current in cells stimulated with 5-HT.

The level of cyclic AMP in NCB-20 cells was increased by 5-HT, 5-methoxytryptamine and 2-methyl-5-HT with EC$_{50}$ of 0.5±0.1, 1.0±0.1, 10±0.1 μM, respectively. The 5-HT-mediated increase of cyclic AMP content was completely blocked by metergoline but unaffected by 5-HT$_3$ antagonists, ICS 205-930, MDL 72222, quipazine and 5-HT$_2$ antagonist, ketanserin. Putative 5-HT$_{1A}$ agonists (8-OH-DPAT, ipsapirone and buspirone) and 5-HT$_{1B}$ agonists (TFMPP and m-CPP) affected neither basal nor forskolin-dependent cyclic AMP accumulation. Receptor binding studies suggest that NCB-20 cells are devoid of 5-HT$_{1A}$ and 5-HT$_{1B}$ receptor sites. Application of 5-HT onto NCB-20 cells resulted in membrane depolarization by an evoked inward current which displayed rapid desensitization. 5-HT-mediated current had a reversal potential around 0 mV and was potently and reversibly inhibited by ICS 205-930. Our data suggest that in NCB-20 cells, the 5-HT$_3$ receptor is involved in the generation of inward currents, while the 5-HT receptor coupled to adenylate cyclase does not seem to correspond to any of the known receptor subtypes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01559-08 BCG

PERIOD COVERED

October 1, 1988 through September 30, 1989

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Peptides in the Brain and Spinal Cord: Function and Distribution

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

PI:	H. Y.T. Yang	Section Chief	BCG, NIMH
Other:	E.A. Majane	Chemist	BCG, NIMH

COOPERATING UNITS (if any)

1) Pertti Panula, M.D., Dept. of Anatomy, Univ. of Helsinki, Helsinki, Finland
2) M. Kavaliers, University of Houston Clear Lake, Houston, Texas

LAB/BRANCH

Laboratory of Biochemical Genetics

SECTION

Neuropeptides

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, DC 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	0.5	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  ☐ (a1) Minors
  ☐ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

The octapeptide Phe-Leu-Phe-Gln-Arg-Phe-NH_2 (F-8-F-NH_2) was initially detected by antiserum raised against the molluskan cardioexcitatory peptide Phe-Met-Arg-Phe-NH_2 and subsequently isolated from bovine brain. F-8-F-NH_2 can decrease morphine analgesia and is highly localized in the substantia gelatinosa of the dorsal spinal cord, area important for the opiate-mediated analgesia. These observations suggest that F-8-F-NH_2 may function as an endogenous opiate antagonist. In this study the functional role of F-8-F-NH_2 was further investigated. IgG prepared from F-8-F-NH_2 antiserum was found to increase the durations and levels of morphine- and immobilization-induced analgesia in a naloxone-reversible manner. In the rat, F-8-F-NH_2 immunoreactivity was detected in the CSF and the level of this immunoreactivity was increased significantly in the rat rendered morphine tolerant. These results provide further evidence that F-8-F-NH_2 functions as an endogenous opiate antagonist and has a role in the mediation of antinociception. In the rat pituitary, a very high content of F-8-F-NH_2 immunoreactivity was found in nerve terminal-like structures in the posterior lobe, indicating a possible endocrine function for F-8-F-NH_2. Interestingly, F-8-F-NH_2 immunoreactivity was found to be deficient in the pituitary of the Bratlleboro rat, which lacks arg^8-vasopressin. Whether the secretion of F-8-F-NH_2 in the pituitary gland is regulated by arg^8-vasopressin is under current investigation.

The proposed course of this study is to study 1) the function of F-8-F-NH_2 in the pituitary, 2) the effects of F-8-F-NH_2 on opiate-mediated responses such as abstinence syndrome and opiate mediated feeding, and 3) the isolation and characterization of other FMRF-NH_2-like material from mammalian brains.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH00941-09 LBCG

PERIOD COVERED
October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Biochemical Genetics and Metabolic Diseases.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C.R.Merril	Chief, Biochemical Genetics	BCG, NIMH
Others:	M.Polymeropolous	Visiting Associate	BCG, NIMH
	S.Charya	Staff Associate	BCG, NIMH
	Janet Joy	Staff Fellow	BCG, NIMH
	Richard Poglod	Staff Associate	BCG, NIMH

COOPERATING UNITS *(if any)*
California Institute of Technology, University of Virginia, Charlottesville, Monoclonetics, Houston Texas.

LAB/BRANCH
Biochemical Genetics Branch

SECTION
Biochemical Genetics Section

INSTITUTE AND LOCATION
NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.5	3.5	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects
☐ (a1) Minors
☐ (a2) Interviews

XX ☐ (b) Human tissues [Human tissues]

☐ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The high resolution and detection which is now available with two dimensional electrophoresis and silver staining permits its development as a "non-biased" diagnostic tool. That is, since more than a thousand protein gene products can be examined in almost any tissue or body fluid sample it is likely that some of these will be affected by disease states. The patterns of qualitative and quantitative alterations may provide new diagnostic capabilities and insights into the underlying pathophysiological processes. Proteins which appear to be abnormal in disease states can often be sequenced and identified by comparisions with existing databases or partial sequences can be used as an aid in isolating the gene of origin.

The crosslinking agents, electrophoretic, and silver staining protocol developed by the laboratory have increased the resolution and reproducibility of the electrophoretic techniques. The laboratory is now expanding its studies of clinically relevent diseases.

Applications of these methodologies in studies of protein patterns in spinal fluid have led to the discovery of diagnostic proteins for Creutzfeldt-Jakob disease, Parkinson's disease, and the presence of two abnormal proteins in more than 1/3 of the schizophrenic patients in our studies. Diagnostic proteins have also been found with these technologies in a number of other diseases by other groups, including certain forms of leukemia. The Laboratory plans to expand our examination of disease and physiological states.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00935-22 LBCG

PERIOD COVERED

October 1, 1988 to September 30, 1989

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of Plasmids and Small Genomes in Human Cells.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C.R.Merril	Chief, Biochemical Genetics	BCG, NIMH
Others:	L. Mitchell	Staff Fellow	BCG, NIMH
	D. Rath	Staff Biologist	BCG, NIMH
	B. Budowle	Chief, Forensic Sci.Research	FBI, Academy
	T. Sunderland	Senior Staff	LCS, NIMH
	R. O'Neill	Staff Fellow	DMN, NINCDS

COOPERATING UNITS *(if any)*

Forensic Science Research Group, FBI Academy, Quantico, Virginia

LAB/BRANCH

Biochemical Genetics Branch

SECTION

Biochemical Genetics Section

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.25	1.25	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects XX ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Laboratory has been working on methods to examine the intra-individual somatic heterogeneity of the mitochondrial genome in normal and diseased tissue. As the mitochondrial genome is the main site of oxidation and the generation of free radical and since there are few if any repair mechanisms for the mit-DNA we suspect that there may be a significant level of somatic mutations in certain postmitotic tissues. The mitochondrial genome in tissues under oxidative stress, such as the brain and muscle, may be the most vulnerable to mutagenesis. To examine this possibility, the laboratory has developed a rapid method of DNA sequencing by employing the polymerase chain reaction and an amplification primer with a 5' biotinylated ligand to provide for a simplified method of preparing single stranded DNA which is easily sequenced by the Sanger technique. This procedure has facilitate molecular studies of the mit-genome and should prove generally useful for the study and diagnosis of human genetic diseases. le have also been studying methods of adapting RNA:DNA duplexes for the rapid screening of genomic variations: nismatches, substitutions and deletions.

Jhen restriction fragment analysis was first applied to the mitochondrial genome it was concluded that the genome ias monoclonal in each individual, with little if any evidence of somatic mutations. However, over the past two ears large(7kb) deletion mutations have been observed in muscle mitochondria while the leukocyte mitochondrial were ntact in some individuals with mitochondrial myopathies and related clinical disorders. Mutational events in the nitochondrial genome may provide some explanations for the pathophysiology associated with certain diseases and ging.

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